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Halomethanes: Ambient Water Quality Criteria

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HALOMETHANES

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for halmethanes. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgement. It does not reflect consi....

KEYWORDS: *Water quality, *Toxicology, *Halogen organic, *Toxic substances, *Water pollution effects(Humans).

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CRITERION DOCUMENT

HALOMETHANES

Criteria

Aquatic Life

Methyl Chloride

For methyl chloride the criterion to protect freshwater aquatic life as derived using procedures other than the Guidelines is 7,000 µg/l as a 24-hour average and the concentration should never exceed 16,000 µg/l at any time.

For methyl chloride the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 3,700 µg/l as a 24-hour average and the concentration should never exceed 8,400 µg/l at any time.

Methyl Bromide

For methyl bromide the criterion to protect freshwater aquatic life as derived using procedures other than the Guidelines is 140 µg/l as a 24-hour average and the concentration should never exceed 320 µg/l at any time.

For methyl bromide the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 170 µg/l as a 24-hour average and the concentration should never exceed 380 µg/l at any time.

Methylene Chloride

For methylene chloride the criterion to protect freshwater aquatic life as derived using procedures other than the Guidelines is 4,000 µg/l as a 24-hour average and the concentration should never exceed 9,000 µg/l at any time.

For methylene chloride the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 1,900 µg/l as a 24-hour average and the concentration should never exceed 4,400 µg/l at any time.

Bromoform

For bromoform the criterion to protect freshwater aquatic life as derived using procedures other than the Guidelines is 840 µg/l as a 24-hour average and the concentration should never exceed 1,900 µg/l at any time.

For bromoform the criterion to protect saltwater aquatic life as derived using the Guidelines is 180 µg/l as a 24-hour average and the concentration should never exceed 420 µg/l at any time.

Human Health

For the protection of human health from the toxic properties of halomethanes ingested through water and through contaminated aquatic organisms, the ambient water criteria for the halomethanes discussed in this document are:

Compound	Criterion Level (µg/l)
Chloromethane (Methyl Chloride)	2
Bromomethane (Methyl Bromide)	2
Dichloromethane (Methylene Chloride)	2
Bromodichloromethane	2
Tribromomethane (Bromoform)	2
Dichlorodifluoromethane	3,000
Trichlorofluoromethane	32,000

Introduction

The halomethanes are a subcategory of halogenated hydrocarbons. This document reviews the following halomethanes: chloromethane, bromomethane, methylene chloride, bromoform, bromodichloromethane, trichlorofluoromethane, and dichlorodifluoromethane.

Methyl chloride is also known as chloromethane (Windholz, 1976). It is a colorless, flammable, almost odorless gas at room temperature and pressure. It is used as a refrigerant, a methylating agent, a dewaxing agent, and catalytic solvent in synthetic rubber production (MacDonald, 1964). Methyl bromide has been referred to as bromomethane, monobromomethane, and embafume (Windholz, 1976). It has been widely used as a fumigant, fire extinguisher, refrigerant, and insecticide (Kantarjian and Shaheen, 1963). Today the major use of methyl bromide is as a fumigating agent, and this use has caused sporadic outbreaks of serious human poisoning.

Methylene chloride has been referred to as dichloromethane, methylene dichloride, and methylene bichloride (Windholz, 1976). It is a common industrial solvent found in insecticides, metal cleaners, paints, and paint and varnish removers (Balmer, et al. 1976). In 1976, 244,129 metric tons (538,304,000 lbs) were produced in the United States with an additional 19,128 metric tons (42,177,000 lbs) imported (U.S. EPA, 1977a).

Trichlorofluoromethane is also known as trichloromonofluoromethane, fluorotrichloromethane, Frigen 11, Freon 11, and Arcton 9. Dichlorodifluoromethane has been referred to as difluorodichloromethane, Freon 12, Frigen 12, Arcton 6, Genetron 12, Halon, and Isotron 2. Freon compounds are organic compounds which contain fluorine. They have many desirable characteristics which include a high degree of chemical stability and relatively low toxicity, and they are nonflammable. Freon compounds have found many applications ranging from use as propellants to refrigerants and solvents (Van Auken, et al. 1975).

Bromoform is also known as tribromomethane (Windholz, 1976). It is used in pharmaceutical manufacturing, as an ingredient in fire resistant chemicals and gauge fluid, and as a solvent for waxes, grease, and oils (U.S. EPA, 1975a). Bromodichloromethane is used as a reagent in research (Natl. Acad. Sci. 1978).

The physical characteristics of the halomethanes are listed in Table 1. Monohalomethanes can be hydrolyzed slowly in neutral waters forming methanol and hydrogen halide. The rate of hydrolysis increases with size of the halogen moiety (Boggs and Mosher, 1960). Zafiriou (1975) has indicated that in seawater iodomethane can react with chloride ion to yield chloromethane and this reaction occurs as fast as the exchange of iodomethane into the atmosphere (exchange rate, 4 x 10^{-7}/sec). The monohalomethanes are not oxidized readily under ordinary conditions. Bromomethane at 14.5 percent concentrations in air and intense heat will produce

TABLE 1

Physical Characteristics of Halomethanes

Compound	Molecular weight	Physical state under ambient conditions	mp. (°C)	bp. (°C)	Specific gravity	Vapor pressure (mm Hg)	Solubility in water (ug/l)	Solubility in organic solvents
chloromethane	50.49[a]	colorless gas[a]	-97.73[a]	-24.2[a]	0.973(-10°C)[b]		$5.38x10^{6}$	alcohol, ether acetone, benzene, chloroform, acetic acid[a]
bromomethane	94.94[a]	colorless gas[a]	-93.6[a]	3.56[a]	1.737(-10°C)[b]		$1x10^{6}$	alcohol, ether, acetic acid[a]
dichloromethane	84.93[a]	colorless liquid[a]	-95.1[a]	40[a]	1.327(20°C)[a]	362.4(20°C)[c]	$13.2x10^{6}$[c] (25°C)	alcohol, ether[a]
trichlorofluoromethane	137.37[a]	colorless liquid[a]	-111[a]	23.82[a]	1.467(25°C)[a]	667.4(20°C)[c]	$1.1x10^{6}$[c] (20°C)	alcohol, ether[d]
dichlorodifluoromethane	120.91[a]	colorless gas[a]	-158[a]	-29.79[a]	1.75(-115°C)[a]	4,306(20°C)[c]	$2.8x10^{5}$[c] (25°C)	alcohol, ether[a]
tribromomethane	252.75[a]	colorless liquid[a]	8.3[a]	149.5[a]	2.890(20°C)[a]		slightly sol.[a]	alcohol, ether, benzene, chloroform, ligroin[a]
bromodichloromethane	163.83[a]	colorless liquid[a]	-57.1[a]	90[a]	1.980(20°C)		insoluble[a]	alcohol, ether, acetone, benzene, chloroform[a]

a) Weast, 1972
b) U.S. EPA, 1977b
c) Pearson and McConnell, 1975
d) Windholz, 1976

a flame (Stenger and Atchison, 1964). Chloromethane in contact with a flame will burn, producing CO_2 and HCl (Hardie, 1964). Monohalomethanes undergo photolysis in the upper atmostphere where ultraviolet radiation is of sufficient energy to initiate a reaction (Basak, 1973).

Prolonged heating of dichloromethane with water at 180°C results in the formation of formic acid, methyl chloride, methanol, hydrochloric acid and some carbon monoxide. In contact with water at elevated temperatures, methylene chloride corrodes iron, some stainless steels, copper, and nickel (Hardie, 1964).

Trichlorofluoromethane is nonflammable. Decomposition of tribromomethane is accelerated by air and light (Windholz, 1976).

Chloromethane has been demonstrated to be toxic to aquatic organisms at levels of 270,000 to 550,000 ug/l (96 hr. LC50 values) in controlled laboratory tests (Dawson, et al. 1977). Corresponding acute toxicity values for bromomethane range from 11,000 to 12,000 ug/l (Dawson, et al. 1977). Dichloromethane LC50 values range from 224,000 to 331,000 ug/l (U.S. EPA, 1978) and tribromomethane LC50 values range from 17,900 to 46,500 ug/l (U.S. EPA, 1978). The latter compound demonstrates aquatic organism chronic toxicity effects at 14,000 to 24,000 ug/l (U.S. EPA, 1978).

The toxic nature of methyl chloride on humans is thought to act on the central nervous system. In a mild to moderate intoxication, the symptoms consist of blurring of vision, headache, vertigo, loss of coordination, slurring of speech, staggering, mental confusion, nausea, and vomiting. A severe exposure involves rapid loss of consciousness leading to death (MacDonald, 1964).

Chloromethane is highly mutagenic to the bacteria, *Salmonella typhimurium* TA 1535 (Andrews, et al. 1976) and to the bacteria, *Salmonella typhimurium* TA 100 (Simmon, et al. 1977).

Inhalation of bromomethane is the usual route of systemic poisoning, but gastrointestinal absorption is a possibility (Collins, 1965). Following exposure, irritation of eyes and mucous membranes may be noticeable. Within a few hours, malaise, headache, and nausea develop. After 2 to 16 hours, the more serious symptoms develop, including visual disturbance, speech disturbance, irrational behavior, drunkenness, and drowsiness. Under serious exposure, neurologic and psychiatric abnormalities may persist for months or years (Collins, 1965).

As with chloromethane, bromomethane has been reported to be mutagenic in *Salmonella* bacterial test systems (Simmon, et al. 1977).

In non-human mammals, methylene chloride inhalation at levels of 1,000 and 5,000 ppm (3,477 and 17,383 mg/m^3) for not more than 14 hours resulted in severe weight losses, liver injury, hepatic failures, and death (Haun, et al. 1971). In humans, methylene chloride is a central nervous system depressant resulting in narcosis at high concentrations (Berger and Fodor, 1969). Inhalation levels of 500 to 1,000 ppm (1,738 to 3,477 mg/m^3) resulted in elevated carboxyhemoglobin saturation levels as well as signs and symptoms of central nervous system depression (Stewart, et al. 1972).

Dichloromethane demonstrated mutagenic properties in Salmonella typhimurium TA 100 and in immunosuppressed mice (Simmon, et al. 1977). The compound also demonstrated a carcinogenic response in mice (Theiss, et al. 1977; Theiss, 1978) but the significance of results from this test are open to question. The carcinogenicity of dichloromethane was reported to be under study by the National Cancer Institute (1977).

Trichlorofluoromethane has completely inhibited the growth of several species of microorganisms at vapor concentrations of 5.62×10^4 to 5.62×10^6 mg/m^3 (Van Auken, et al. 1975). In atmospheric ambient conditions of a 1:1 mixture of oxygen and dichlorodifluoromethane, a significant increase in the mutation rate of the yeast, Neurospora crassa, was noted (Stephens, et al. 1971). Slater (1965) administered trichlorofluoromethane to the stomach of rats and noted no effect on serum-β-glucuronidase activity or liver NADPH levels. Taylor (1975) noted that exposure to 7 percent oxygen-15 percent trichlorofluoromethane caused cardiac arrhythmias in all rabbits exposed. Only a slight hyperglycemia with hyperlactacidema was noted in rats, rabbits, and dogs exposed to ambient atmospheric conditions of 5 percent trichlorofluoromethane (Paulet, et al. 1975). In dogs, trichlorofluoromethane caused a depression of myocardial function (Aviado and Belej, 1975) and in the upper respiratory tract lead to an initial apnea, bradycardia, and a fall in aortic blood pressure (Aviado, 1971). Azar, et al. (1972), noted that human inhalation of 1,000 ppm (4,949 mg/m^3) dichlorodifluoromethane did not reveal any adverse effect, while exposure to 10,000 ppm (49,489 mg/m^3) resulted only in a 7 percent reduction in a standardized psychomotor test score.

Tribromomethane is considered to be highly toxic to both non-human mammalian species and humans. The compound has been shown to be mutagenic in the Salmonella typhimurium TA 100 and Ta 1535 test systems (Simmon, et al. 1977) and carcinogenic in mice (Theiss, et al. 1977; Theiss, 1978) with the same qualifications for result significance as for dichloromethane noted. Cantor, et al. (1977), have reported positive correlations between cancer mortality rates and levels of brominated trihalomethanes in drinking water in epidemiological studies.

Bromodichloromethane is acutely toxic to mice (Bosman, et al. 1978). It was mutagenic in the Salmonella typhimurium TA 100 bacterial test system (Simmon, et al. 1977) and carcinogenic in mice (Theiss, et al. 1977; Theiss, 1978) with the same qualification for result significance as for dichloromethane noted. Cantor, et al. (1977), have reported positive correlations between cancer mortality rates and levels of brominated trihalomethanes in drinking water in epidemiological studies.

The relatively high water solubilities of chloromethane and bromomethane and their relatively high vapor pressures indicate that they have a low potential to bioconcentrate in aquatic species. By using the equation of Metcalf and Lu (1973), the predicted bioconcentration factors are 2 and 6, respectively.

Methylene chloride is a major halogenated pollutant with a large potential for delivery of chlorine to the stratosphere. The photooxidation of the compound in the troposphere probably proceeds with a half-life of several months, similar to the case of methyl chloride. The principal oxidation product of methylene chloride is phosgene which results from the two hydrogens being abstracted from the molecule. It is conceivable that this phosgene may be photolyzed to yield chlorine atoms in the ozone-rich region of the stratosphere. It thus appears that there is some potential for ozone destruction by methylene chloride since the generated chlorine atoms will attack ozone (U.S. EPA, 1975b).

Similarly, fully halogenated substances such as trichlorofluoromethane and dichlorodifluoromethane migrate to the stratosphere where they are photodissociated, adversely affecting the ozone balance (U.S. EPA, 1975b). Trichlorofluoromethane does not significantly bioconcentrate in aquatic organims (Dickson and Riley, 1976).

There are few data in the literature relating to the environmental fate or degradation of bromodichloromethane and tribromomethane.

REFERENCES

Andrews, A.W., et al. 1976. A comparison of the mutagenic properties of vinyl chloride and methyl chloride. Mutat. Res. 40: 273.

Aviado, D.M. 1971. Cardiopulmonary effects of fluorocarbon compounds. Aerospace Med. Res. Lab. Wright Patterson Air Force Base, Ohio.

Aviado, D.M., and M.A. Belej. 1975. Toxicity of aerosol propellants in the respiratory and circulatory systems. Ventricular function in the dog. Toxicology 3: 79.

Azar, A., et al. 1972. Experimental human exposure to fluorocarbon 12 (dichlorodifluoromethane). Am. Ind. Hyg. Assoc. Jour. 33: 207.

Balmer, M.F., et al. 1976. Effects in the liver of methylene chloride inhaled alone and with ethyl alcohol. Am. Ind. Hyg. Assoc. Jour. 37: 345.

Basak, A.K. 1973. The photolytic decomposition of methyl chloride. Jour. Ind. Chem. Soc. 50: 767.

Berger, M., and G.G. Fodor. 1969. Zentralrervose storunger inter Einfluso dichloromethanhaltiger Luftgemische-2bl. Bakt., Abt. 1, Ref. 215, 1963, 503.

Boggs, J.E., and H.P. Mosher. 1960. Effect of fluorine substitution on the rate of hydrolysis of chloromethane. Jour. Am. Chem. Soc. 82: 3517.

Bowman, F.G., et al. 1978. The toxicity of some halomethanes in mice. Toxicol. Appl. Pharmacol. 44: 213.

Cantor, K.P., et al. 1977. Associations of halomethanes in drinking water with cancer mortality. Jour. Natl. Cancer Inst. (In press.)

Collins, R.P. 1965. Methyl bromide poisoning. Calif. Med. 103: 112.

Dawson, G.W., et al. 1977. The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes. Jour. Hazard. Mater. 1: 303.

Dickson,.A.G., and J.P. Riley. 1976. The distribution of short-chain halogenated aliphatic hydrocarbons in some marine organisms. Mar. Pollut. Bull 7: 167.

Hardie, D.W.F. 1964. Methyl chloride. Kirk-Othmer Encyclopedia of Chemical Technology. 2nd ed. Interscience Publishers, New York.

Haun, C.C., et al. 1971. Continuous animal exposure to methylene chloride. Aerospace Med. Res. Lab. Wright Patterson Air Force Base, Ohio.

Kantarjian, A.D., and A.S. Shaheen. 1963. Methyl bromide poisoning with nervous system manifestations resembling polyneuropathy. Neurology 13: 1054.

MacDonald, J.D.C. 1964. Methyl chloride intoxication. Jour. Occup. Med. 6: 81.

Metcalf, R.L., and P.Y. Lu. 1973. Environmental distribution and metabolic fate of key industrial pollutants and pesticides in a model ecosystem. Univ. Ill. Water Resour. Center, UILU-WRC-0069. PB 225479, Natl. Tech. Inf. Serv., Springfield, Va.

National Academy of Sciences. 1978. Nonfluorinated halomethanes in the environment. Washington, D.C.

National Cancer Institute. 1977. Chemicals being tested for carcinogenicity by the bioassay program. Rep. Tech. Inf. Resour. Branch, Natl. Cancer Inst., U.S. Dep. Health Educ. Welfare, Bethesda, Md.

Paulet, G., et al. 1975. Fluorocarbons and general metabolism in the rat, rabbit, and dog. Toxicol. Appl. Pharmacol. 34: 197.

Pearson, C.R., and G. McConnell. 1975. Chlorinated C1 and C2 hydrocarbons in the marine environment. Proc. R. Soc. London B. 189: 305.

Simmon, V.F., et al. 1977. Mutagenic activity of chemicals identified in drinking water. Presented at 2nd Int. Conf. Environ. Mutagens. Edinburgh, Scotland. July, 1977.

Slater, T.F. 1965. A note on the relative toxic activities of tetrachloromethane and trichlorfluoromethane on the rat. Biochem. Pharmacol. 14: 178.

Stenger, V.A., and G.J. Atchison. 1964. Methyl bromide. Kirk-Othmer Encyclopedia of Chemical Technology. 2nd ed. Interscience Publishers, New York.

Stephens, S., et al. 1971. Phenotypic and genetic effects of Neurospora crassa produced by selected gases and gases mixed with oxygen. Dev. Ind. Microbiol. 12: 346.

Stewart, R.D., et al. 1972. Experimental human exposure to methylene chloride. Arch. Environ. Health 25: 342.

Taylor, G.J. 1975. Cardiac arrhythmias in hypoxic rabbits during aerosol propellant inhalation. Arch. Environ. Health 30: 349.

Theiss, J.C. 1978. Personal communication.

Theiss, J.C., et al. 1977. Test for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in strain A mice. Cancer Res. 37: 2717.

U.S. EPA. 1975a. Initial scientific and minieconomic review of folpet. Draft. Rep. Off. Pestic. Prog. Washington, D.C.

U.S. EPA. 1975b. Report on the problem of halogenated air pollutants and stratospheric ozone. EPA 600/9-75-008. Washington, D.C.

U.S. EPA. 1977a. Area 1. Task 2. Determination of sources of selected chemicals in waters and amounts from these sources. Draft final rep. Contract No. 68-01-3852. Washington, D.C.

U.S. EPA. 1977b. Investigation of selected potential environmental contaminants. Monohalomethanes. EPA 560/2-77-007. Washington, D.C.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. Contract No. 68-01-4646. Washington, D.C.

Van Auken, et al. 1975. Comparison of the effects of three fluorocarbons on certain bacteria. Can. Jour. Microbiol. 21: 221.

Weast, R.C., ed. 1972. Handbook of chemistry and physics. CRC Press, Cleveland, Ohio.

Windholz, M., ed. 1976. The Merck Index. Merck and Co., Rahway, N.J.

Zafiriou, O.C. 1975. Reaction of methyl halides with seawater and marine aerosols. Jour. Mar. Res. 33: 75.

AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

Although the aquatic toxicity data base for halomethanes is limited, it allows some generalization concerning trends within the class. Data on chloroform and carbon tetrachloride are included for discussion and are also treated in separate criterion documents. Methylene chloride, methyl chloride, bromoform, and methyl bromide are the only other halomethanes for which appropriate data are available.

Acute Toxicity

Apparently, the brominated compounds are more toxic to fish than the chlorinated analogs (Table 1). This pattern is repeated for the saltwater fish (Table 4). The unadjusted 96-hour LC50 values for bluegill are 11,000 µg/l, and 550,000 µg/l for methyl bromide and methyl chloride, respectively, under static (renewal) test conditions (Dawson, et al. 1977). For bromoform and chloroform the 96-hour LC50 values are

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

29,300 µg/l (U.S. EPA, 1978) and 115,000 µg/l to 100,000 µg/l, respectively. The data on acute static tests with bluegill show a correlation between increasing chlorination and toxicity. The 96-hour LC50 values are 550,000 µg/l (Dawson, et al. 1977) for methyl chloride, 244,000 µg/l for methylene chloride (U.S. EPA, 1978), 100,000 to 115,000 µg/l for chloroform (Bentley, et al. 1975), and 125,000 µg/l (Dawson, et al. 1977) and 27,300 µg/l (U.S. EPA, 1978) for carbon tetrachloride. Alexander, et al. (1978) compared the effect of test procedures on the toxicity of methylene chloride to the fathead minnow. The flow-through test result was 193,000 µg/l and the static test result was 310,000 µg/l (Table 1). After adjustment according to the Guidelines the latter LC50 value becomes 169,477 µg/l, very similar to the flow-through result, supporting the appropriateness of the adjustment factors for test conditions and methylene chloride. The Final Fish Acute Values for bromoform, methylene chloride, methyl bromide, and methyl chloride are 4,100, 38,000, and 1.500, and 77,000 µg/l, respectively.

The 48-hour EC50 values are 224,000, 28,900, and 35,200 µg/l for methylene chloride (Table 2), chloroform, and carbon tetrachloride, respectively (U.S. EPA, 1978). The result with chloroform (28,900 µg/l) does not support any conclusion about the correlation of toxicity and amount of chlorination for the data with Daphnia magna. For bromoform and methylene chloride, there appears to be little difference is sensitivity between Daphnia magna and the bluegill. The LC50 and EC50 values are both 224,000 µg/l for methylene chloride and 29,300

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The data indicate that the Final Invertebrate Acute Values for halomethanes are lower than the comparable values for fish. The Final Fish and Final Invertebrate Acute Value comparisons are: bromoform - 4,100 and 1,900 µg/l, respectively, methylene chloride - 38,000 and 9,000 µg/l, respectively; chloroform - 11,000 and 1,200 µg/l, respectively; and carbon tetrachloride - 8,200 and 1,400 µg/l, respectively. Thus, when a Final Invertebrate Acute Value exists, it becomes the Final Acute Value.

Chronic Toxicity

No life cycle or embryo-larval tests have been conducted with freshwater organisms and any halomethane other than chloroform and carbon tetrachloride. In those tests, the concentration at which no adverse effects of chloroform were observed for *Daphnia magna* was between 1,800 and 3,600 µg/l, and no adverse effects of carbon tetrachloride were observed on the fathead minnow at the highest test concentration of 3,400 µg/l. Details of these tests may be found in the criterion documents for those chemicals.

Plant Effects

The 96-hour EC50 values for bromoform (Table 3), based on chlorophyll *a* and cell numbers of the alga, *Selenastrum capricornutum*, are 112,000 and 116,000 µg/l, respectively. The same tests with methylene chloride showed the EC50 values were above the highest test concentration, 662,000 µg/l (U.S. EPA, 1978).

Residues

No residue data for freshwater fish are available for halomethanes other than for chloroform and carbon tetrachloride, for which the bioconcentration factors (U.S. EPA, 1978) were 6 and 30, respectively. Details of these tests may be found in the criterion documents for those chemicals.

CRITERION FORMULATION

Freshwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Bromoform

Final Fish Acute Value = 4,100 μg/l

Final Invertebrate Acute Value = 1,900 μg/l

Final Acute Value = 1,900 μg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 110,000 μg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 110,000 μg/l

0.44 x Final Acute Value = 840 μg/l

Methylene Chloride

Final Fish Acute Value = 38,000 μg/l

Final Invertebrate Acute Value = 9,000 μg/l

Final Acute Value = 9,000 μg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = greater than 660,000 μg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = greater than 660,000 μg/l

0.44 x Final Acute Value = 4,000 μg/l

Methyl Bromide

Final Fish Acute Value = 1,500 μg/l

Final Invertebrate Acute Value = not available

Final Acute Value = 1,500 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = not available

0.44 x Final Acute Value = 660 µg/l

Methyl Chloride

Final Fish Acute Value = 77,000 µg/l

Final Invertebrate Acute Value = not available

Final Acute Value = 77,000 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = not available

0.44 x Final Acute Value = 34,000 µg/l

No freshwater criterion can be derived for any halomethane using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available.

However, results obtained with halomethanes and freshwater and saltwater fish and invertebrate species indicate how criteria may be estimated.

For bromoform and methylene chloride with freshwater and saltwater organisms and for chloroform and carbon tetrachloride with freshwater organisms, the Final Invertebrate Acute Value divided by the Final Fish Acute Value is 0.46, 0.24, 0.16, 0.090, 0.11, and 0.17 respectively, for an average of 0.21. Multiplying this value times the Final Acute Values for methyl chloride and methyl bromide with freshwater fish results in estimated freshwater Final Invertebrate Acute Values of 0.21 x 77,000 µg/l = 16,000 µg/l and 0.21 x 1,500 µg/l = 320 µg/l respectively. Thus the Final Acute Values for methyl chloride and methyl bromide would be based on these estimated values and are 16,000 µg/l and 320 µg/l, respectively.

For chloroform and freshwater organisms the Final Chronic Value is about the same as 0.44 times the Final Acute Value, and for bromoform and saltwater organisms the Final Chronic Value is greater than 0.44 times the Final Acute Value, even though a chronic value is available for fish or invertebrates in both other halomethanes and freshwater organisms using 0.44 times the Final Acute Value.

The maximum concentration of bromoform is the Final Acute Value of 1,900 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For bromoform the criterion to protect freshwater aquatic life as derived using procedures other than the Guidelines is 840 µg/l as a 24-hour average and the concentration should never exceed 1,900 µg/l at any time.

The maximum concentration of methylene chloride is the Final Acute Value of 9,000 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For methylene chloride the criterion to protect freshwater aquatic life as derived using procedures other than the Guidelines is 4,000 µg/l as a 24-hour average and the concentration should never exceed 9,000 µg/l at any time.

The estimated maximum concentration of methyl bromide is the Final Acute Value of 320 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For methyl bromide the criterion to protect freshwater aquatic life as derived using procedures other than the Guidelines is 140 µg/l as a 24-hour average and the concentration should never exceed 320 µg/l at any time.

The estimated maximum concentration of methyl chloride is the Final Acute Value of 16,000 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For methyl chloride the criterion to protect freshwater aquatic life as derived using procedures other than the Guidelines is 7,000 µg/l as a 24-hour average and the concentration should never exceed 16,000 µg/l at any time.

Table 1. Freshwater fish acute values for halomethanes

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Bromoform						
Bluegill, *Lepomis macrochirus*	S	U	96	29,300	16,018	U.S. EPA, 1978
Methylene chloride						
Bluegill, *Lepomis macrochirus*	S	U	96	224,000	122,461	U.S. EPA, 1978
Fathead minnow, *Pimephales promelas*	FT	M	96	193,000	193,000	Alexander, et al. 1978
Fathead minnow, *Pimephales promelas*	S	U	96	310,000	169,477	Alexander, et al. 1978
Methyl chloride						
Bluegill, *Lepomis macrochirus*	R	U	96	550,000	300,685	Dawson, et al. 1977
Methyl bromide						
Bluegill, *Lepomis macrochirus*	R	U	96	11,000	6,014	Dawson, et al. 1977

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* S = static, FT = flow-through, R = renewal

** U = unmeasured, M = measured

Geometric mean of adjusted values - Bromoform = 16,018 μg/l $\frac{16,018}{3.9}$ = 4,100 μg/l

Methlyene chloride = 148,822 μg/l $\frac{148,822}{3.9}$ = 38,000 μg/l

Methyl chloride = 300,685 μg/l $\frac{300,685}{3.9}$ = 77,000 μg/l

Methyl bromide = 6,014 μg/l $\frac{6,014}{3.9}$ = 1,500 μg/l

Table 2. Freshwater invertebrate acute values for halomethanes (U.S. EPA, 1978)

Organism	Bioassay Method *	Test Conc.**	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)
		Bromoform			
Cladoceran, *Daphnia magna*	S	U	48	46,500	39,386
		Methylene chloride			
Cladoceran, *Daphnia magna*	S	U	48	224,000	189,728

* S = static

** U = unmeasured

Geometric mean of adjusted values - Bromoform = 39,386 µg/l $\frac{39,386}{21}$ = 1,900 µg/l

Methylene chloride = 189,728 µg/l $\frac{189,728}{21}$ = 9,000 µg/l

Table 3. Freshwater plant effects for halomethanes (U.S. EPA, 1978)

Organism	Effect	Concentration (µg/l)
		Bromoform
Alga, *Selenastrum capricornutum*	Chlorophyll *a* EC50 96-hr	112,000
Alga, *Selenastrum capricornutum*	Cell number EC50 96-hr	116,000
		Methylene chloride
Alga, *Selenastrum capricornutum*	Chlorophyll *a* EC50 96-hr	>662,000
Alga, *Selenastrum capricornutum*	Cell number EC50 96-hr	>662,000

Lowest plant value Bromoform = 112,000 µg/l

Methylene chloride = >662,000 µg/l

SALTWATER ORGANISMS

Introduction

Although the aquatic toxicity data base for halomethanes is limited, it allows some generalizations concerning trends within the class. Data on chloroform and carbon tetrachloride are included for discussion and are also treated in separate criterion documents. Methylene chloride, methyl chloride, bromoform, and methyl bromide are the only other halomethanes for which appropriate data are available.

Acute Toxicity

Apparently, the brominated compounds are more toxic to fish than the chlorinated analogs, (Table 4) as is true for the freshwater fish (Table 1). The unadjusted 96-hour LC50 values for the tidewater silversides (Dawson, et al. 1977) and methyl bromide and methyl chloride are 12,000 and 270,000 µg/l, respectively. The Final Fish Acute Values for bromoform, methylene chloride, methyl bromide, and methyl chloride are 2,600, 49,000, 1,800, and 40,000 µg/l, respectively (Table 4).

The mysid shrimp has been tested with bromoform and methylene chloride (U.S. EPA, 1978) and the unadjusted 96-hour LC50 values are 24,400 and 256,000 µg/l, respectively (Table 5). The Final Invertebrate Acute Values, obtained after adjusting the data for test conditions and species sensitivity according to the Guidelines are 420 µg/l for bromoform and 4,400 µg/l for methylene chloride. These concentrations are below the comparable values for fish (Table 4) and, therefore, become the Final Acute Values for bromoform and methylene chloride.

Chronic Toxicity

An embryo-larval test has been conducted with the sheepshead minnow and bromoform (U.S. EPA, 1978) and the chronic value derived from this test is 9,165 µg/l (Table 6). There are no other chronic data for any halomethane. The Final Fish Chronic Value, and Final Chronic Value, for bromoform is 1,400 µg/l.

Plant Effects

The 96-hour EC50 values for bromoform (Table 7), based on chlorophyll a and cell numbers of the alga, Skeletonema costatum, are 12,300 and 11,500, respectively. The same tests with methylene chloride showed the EC50 values were above the highest test concentration, 662,000 µg/l (U.S. EPA, 1978).

Residues

No residue data for saltwater aquatic organisms are available for any halomethane.

CRITERION FORMULATION

Saltwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Bromoform

Final Fish Acute Value = 2,600 µg/l

Final Invertebrate Acute Value = 420 µg/l

Final Acute Value = 420 µg/l

Final Fish Chronic Value = 1,400 µg/l

Final Invertebrate Chronic Value = not available

Final Plant Value = 12,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 1,400 µg/l

0.44 x Final Acute Value = 180 µg/l

Methylene Chloride

Final Fish Acute Value = 49,000 µg/l

Final Invertebrate Acute Value = 4,400 µg/l

Final Acute Value = 4,400 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = greater than 660,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = greater than 660,000 µg/l

0.44 x Final Acute Value = 1,900 µg/l

Methyl Bromide

Final Fish Acute Value = 1,800 µg/l

Final Invertebrate Acute Value = not available

Final Acute Value = 1,800 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = not available

0.44 x Final Acute Value = 790 µg/l

Methyl Chloride

Final Fish Acute Value = 40,000 µg/l

Final Invertebrate Acute Value = not available

Final Acute Value = 40,000 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = not available

0.44 x Final Acute Value = 18,000 µg/l

The maximum concentration of bromoform is the Final Acute Value of 420 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower then the 24-hour average concentration.

CRITERION: For bromoform the criterion to protect saltwater aquatic life as derived using the Guidelines is 180 µg/l as a 24-hour average and the concentration should never exceed 420 µg/l at any time.

No saltwater criterion can be derived for methylene chloride, methyl bromide, or methyl chloride using the Guidelines because no

Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available.

However, results obtained with halomethanes and freshwater and saltwater fish and invertebrate species indicate how criteria may be derived.

For bromoform and methylene chloride with freshwater and saltwater organisms and for chloroform and carbon tetrachloride with freshwater organisms, the Final Invertebrate Acute Value divided by the Final Fish Acute Value is 0.46, 0.24, 0.16, 0.090, 0.11, and 0.17 respectively, for an average of 0.21. Multiplying this value times the Final Acute Values for methyl chloride and methyl bromide with saltwater fish results in estimated saltwater Final Invertebrate Acute Values of 0.21 x 40,000 µg/l = 8,400 µg/l and 0.21 x 1,800 µg/l = 380 µg/l, respectively. Thus the Final Acute Values for methyl chloride and methyl bromide would be based on these estimated values and are 8,400 µg/l and 380 µg/l, respectively.

For chloroform and freshwater organisms the Final Chronic Value is about the same as 0.44 times the Final Acute Value, and for bromoform and saltwater organisms the Final Chronic Value is greater than 0.44 times the Final Acute Value, even though a chronic value is available for fish or invertebrate species in both cases. Therefore, it seems reasonable to estimate criteria for other halomethanes and saltwater organisms using 0.44 times the Final Acute Value.

The maximum concentration for methylene chloride is the Final Acute Value of 4,400 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For methylene chloride the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 1,900 µg/l as a 24-hour average and the concentration should never exceed 4,400 µg/l at any time.

The estimated maximum concentration of methyl bromide is the Final Acute Value of 380 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For methyl bromide the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 170 µg/l as a 24-hour average and the concentration should never exceed 380 µg/l at any time.

The estimated maximum concentration of methyl chloride is the Final Acute Value of 8,400 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For methyl chloride the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 3,700 µg/l as a 24-hour average and the concentration should never exceed 8,400 µg/l at any time.

Table 4. Marine fish acute values for halomethanes

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Bromoform						
Sheepshead minnow, *Cyprinodon variegatus*	S	U	96	17,900	9,786	U.S. EPA, 1978
Methylene chloride						
Sheepshead minnow, *Cyprinodon variegatus*	S	U	96	331,000	180,958	U.S. EPA, 1978
Methyl bromide						
Tidewater silversides, *Menidia beryllina*	R	U	96	12,000	6,560	Dawson, et al. 1977
Methyl chloride						
Tidewater silversides, *Menidia beryllina*	R	U	96	270,000	147,610	Dawson, et al. 1977

* S = static, R = renewal

** U = unmeasured

Geometric mean of adjusted values: Bromoform = 9,786 μg/l $\frac{9,786}{3.7}$ = 2,600 μg/l

Methylene chloride = 180,958 μg/l $\frac{180,958}{3.7}$ = 49,000 μg/l

Methyl bromide = 6,560 μg/l $\frac{6,560}{3.7}$ = 1,800 μg/l

Methyl chloride = 147,610 μg/l $\frac{147,610}{3.7}$ = 40,000 μg/l

Table 5. Marine invertebrate acute values for halomethanes (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)
			Bromoform		
Mysid shrimp, *Mysidopsis bahia*	S	U	96	24,400	20,667
			Methylene chloride		
Mysid shrimp, *Mysidopsis bahia*	S	U	96	256,000	216,832

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* S = static

** U = unmeasured

Geometric mean of adjusted values: Bromoform = 20,667 µg/l $\frac{20,667}{49}$ = 420 µg/l

Methylene chloride = 216,832 µg/l $\frac{216,832}{49}$ = 4,400 µg/l

Table 6. Marine fish chronic values for halomethane (U.S. EPA, 1978)

Organism	Test*	Limits (µg/l)	Chronic Value (µg/l)
		bromoform	
Sheepshead minnow, *Cyprinodon variegatus*	E-L	14,000- 24,000	9,165

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* E-L = embryo-larval

Geometric mean chronic value for bromoform = 9,165 µg/l $\frac{9,165}{6.7}$ = 1,400 µg/l

Lowest chronic value for bromoform = 9,165 µg/l

Table 7. Marine plant effects for halomethanes (U.S. EPA, 1978)

Organism	Effect	Concentration (µg/l)
	Bromoform	
Alga, *Skeletonema costatum*	Chlorophyll *a* EC50	12,300
Alga, *Skeletonema costatum*	Cell number EC50	11,500
	Methylene chloride	
Alga, *Skeletonema costatum*	Chlorophyll *a* EC50	>662,000
Alga, *Skeletonema costatum*	Cell number EC50	>662,000

Lowest plant value: Bromoform = 11,500 µg/l

Methylene chloride = >662,000 µg/l

REFERENCES

Alexander, H.C., et al. 1978. Toxicity of perchloroethylene, trichloroethylene, 1,1,1-trichloroethane, and methylene chloride to fathead minnows. Bull. Environ. Contam. Toxicol. 20: 344.

Bentley, R.E., et al. 1975. Acute toxicity of chloroform to bluegill (Lepomis macrochirus), rainbow trout, (Salmo gairdneri), and pink shrimp (Penaeus duorarum). Contract No. WA-6-99-1414-B. U.S. Environ. Prot. Agency.

Dawson, G.W., et al. 1977. The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes. Jour. Hazard Mater. 1: 303.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. Contract No. 68-01-4646. Washington, D.C.

Mammalian Toxicology and Human Health Effects

EXPOSURE

Introduction

The halomethanes are a subclass of halogenated aliphatic hydrocarbon compounds, some of whose members constitute important or potentially hazardous environmental contaminants. The seven halomethane compounds selected for discussion in this document are listed in Table 1. Many other halogenated methane derivative chemicals exist, including various combinations of halogen (bromine, chlorine, fluorine, iodine) substitutions on one, two, three, or all four of the hydrogen positions of methane. Of these, two other particularly important halomethanes, trichloromethane (chloroform) and tetrachloromethane (carbon tetrachloride) are subjects of separate criteria documents. Several recent reviews are available which present extensive discussions of health effects related to halomethane exposure (Natl. Acad. Sci., 1978; Davis, et al. 1977; Howard, et al. 1974).

Humans are exposed to halomethanes by any of three primary routes: (a) intake in water or other fluids, (b) ingestion in food; and (c) inhalation. In certain circumstances (e.g., occupational), exposure by skin absorption may be significant. Halomethanes have been identified in air (Grimsrud and Rasmussen, 1975; Lovelock, et al. 1973; Lovelock, 1975; Singh, et al. 1977; Lillian and Singh, 1974), water (Shackelford and Keith, 1976; Lovelock, 1975; Symons, et al. 1975; Morris and McKay, 1975; Kleopfer, 1976) and food (McConnell, et al. 1975; Monro, et al. 1955), but infor-

TABLE 1

Halomethanes*

Names and CAS Registry Number	Formula
Bromomethane, methyl bromide, monobromomethane, Embafume, Iscobrome, Rotox; 74-83-9	CH_3Br
Chloromethane, methyl chloride, monochloromethane; 74-87-3	CH_3Cl
Dichloromethane, methylene chloride, methane dichloride, methylene dichloride, methylene bichloride; 75-09-2	CH_2Cl_2
Tribromomethane, bromoform, methyl tribromide; 75-25-2	$CHBr_3$
Bromodichloromethane, dichloromethyl bromide; 75-25-4	$BrCHCl_2$
Dichlorodifluoromethane, fluorocarbon 12, F-12, Arcton 6, Freon 12, Frigen 12, Genetron 12, Halon, Isotron 12, difluorodichloromethane; 75-71-8	CCl_2F_2
Trichlorofluoromethane, fluorocarbon 11, F-11, Arcton 9, Freon 11, Frigen 11, Algofrene type 1, trichloromonofluoromethane, fluorotrichloromethane; 75-69-4	CCl_3F

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*Chemical names, common names (underlined), some trade names (capitalized) and synonyms are provided. References: Int. Agency Res. Cancer (1978), Natl. Cancer Inst. (1977), Stecher, et al. (1968), Natl. Library Med. (1978b).

mation concerning relative exposure for specific compounds via the different media is incomplete. Inhalation and/or ingestion of fluids are probably the most important routes of human exposure (Natl. Acad. Sci., 1978).

Presence of the halomethanes in the environment is generally the result of natural, anthropogenic, or secondary sources. The monohalomethanes (bromo-, chloro-, iodomethane) are believed natural in origin with the oceans as a primary source (Lovelock, 1975); natural sources have also been proposed for dichloromethane, tribromomethane, and certain other halomethanes (Natl. Acad. Sci., 1978).

Anthropogenic sources of environmental contamination, such as manufacturing and use emissions are important for several halomethanes. These include: chloromethane (chemical intermediate in production of silicone, gasoline antiknock, rubber, herbicides, plastics, and other materials); bromomethane (soil, seed, feed, and space fumigant agents); dichloromethane (paint remover, solvent, aerosol sprays, plastics processing); tribromomethane (chemical intermediate); bromodichloromethane (used as a reagent in research); dichlorodifluoro methane and trichlorofluoromethane (refrigerant and aerosol propellant uses) (Natl. Acad. Sci., 1978; Davis, et al. 1977; Stecher, et al. 1968).

Secondary sources of halomethanes include such processes as the use of chlorine to treat municipal drinking water and some industrial wastes, and the combustion and thermal degradation of products or waste materials, wherein secondary formation reactions or incidental contamination occur (Natl. Acad. Sci., 1978).

Ingestion from Water

The U.S. Environmental Protection Agency has identified at least ten halogenated methanes in finished drinking waters in the U.S. as of 1975: chloromethane, bromomethane, dichloromethane, dibromomethane, trichloromethane, tribromomethane, bromodichloromethane, dibromochloromethane, dichloroiodomethane, and tetrachloromethane (U.S. EPA, 1975). In the National Organics Reconnaissance Survey in 80 cities, halogenated hydrocarbons were found in finished waters at greater concentrations than in raw waters (Symons, et al. 1975). It was concluded by Symons, et al. (1975) that trihalomethanes (THM) result from chlorination and are widespread in chlorinated drinking waters; concentrations are related to organic content of raw water. Incidence and levels of halomethanes found in the survey are summarized in Table 2.

TABLE 2

Halomethanes in the National Organics Reconnaissance Survey (80 Cities)

Compound	Number of Cities with Positive Results	Concentration, mg/l Minimum	Median	Maximum
Trichloromethane	80	0.0001	0.021	0.311
Bromodichloromethane	78	0.0003	0.006	0.116
Dibromochloromethane	72	0.0004	0.0012	0.110
Tribromomethane	26	0.0008	(a)	0.092
Tetrachloromethane	10	0.002	--	0.003

(a) 98.3 percent of 80 cities had __ 0.005 mg/l tribromomethane
Source: Natl. Acad. Sci., 1978 (data from Symons, et al. 1975)

In its Region V Organics Survey at 83 sites U.S. EPA reported concentrations of several halomethanes in a large percentage of finished municipal waters, as summarized in Table 3. Of the halomethanes detected in drinking waters, dichloromethane, tetrachloromethane, and fully chlorinated higher hydrocarbons probably are not products of water chlorination (U.S. EPA, 1975; Morris and McKay, 1975). Because of its solubility, dichloromethane may exist in water effluents at concentrations of up to 1,500 mg/l, depending on process and terminal treatment factors (Natl. Acad. Sci., 1978).

TABLE 3

Halomethanes in the U.S. EPA Region V Organics Survey (83 Sites)

Compound	Percent of Locations with Positive Results	Concentrations (mg/l) Median	Concentrations (mg/l) Maximum
Bromodichloromethane	78	0.006	0.031
Dibromochloromethane	60	0.001	0.015
Trichloromethane	95	0.020	0.366
Tribromomethane	14	<0.001	0.007
Tetrachloromethane	34*	<0.001*	0.026*
Dichloromethane	8	<0.001	0.007

*A total of 11 samples may have been contaminated by exposure to laboratory air containing tetrachloromethane.

Source: (U.S. EPA, 1975)

U.S. EPA's National Organic Monitoring Survey (NOMS), conducted in 1976 and 1977 (Phases L-III), sampled 113 water supplies representing various sources and treatments (U.S. EPA, 1978a, b). Incidence and concentration data for six halomethanes are summarized in Table 4. Some 63 additional organic compounds or classes were detected, including these halomethanes: bromomethane, dibromomethane, bromochloromethane, iodomethane, dichloroiodomethane, and trichlorofluoromethane. Mean and median total trihalomethane (TTHM) values in 105 to 111 cities over the three phases and sample modes ranged from 0.052 to 0.120 mg/l and 0.038 to 0.087 mg/l, respectively.

Data from a Canadian national survey for halomethanes in drinking water are in general agreement with those from the United States (Health and Welfare Can. 1977). Samples taken from 70 finished water distribution systems showed the following halomethane concentrations:

	Concentration	
	range	median
Chloroform	0 - 121	13 ug/l
Bromodichloromethane	0 - 33	1.4 ug/l
Chlorodibromomethane	0 - 6.2	0.1 ug/l
Tribromomethane	0 - 0.2	0.01 ug/l

As would be expected, based upon previous observations, (Symons, et al. 1975), chlorination as part of the water treatment process led to considerable enhancement of halomethane concentrations, and well sources were associated with much lower halomethane concentrations than river or lake sources. In addition, an unexplained increase in the concentration of halomethanes occurred in the distribution system as compared to halomethane levels in water sampled at the treatment plant.

TABLE 4

Partial summary of National Organics Monitoring Survey, 1976-1977 (U.S. EPA, 1978b)

Compound	Phase	Number of Positive Analyses per Number of Analyses			Mean Concentration, mg/l (Positive Results only)			Median Concentration, mg/l (All Results)		
		I	II	III	I	II	III	I	II	III
Trichloro-methane	Q[+]	102/111*	18/18	98/106	0.047*	0.068	0.038	0.027	0.068	0.022
	T		112/113	101/105		.084	.073		.059	.045
Tribromo-methane	Q	3/111*	6/118	19/106	0.021*	0.028	0.013	<0.003-0.005[a]	<0.0003[a]	<0.0002-0.0006[a]
	T		38/113	30/105		.012	.013		<0.0003[a]	<0.0003-0.0006[a]
Bromodi-chloro-methane	Q	88/111*	18/18	100/106	0.022*	0.016	0.0092	0.0096	0.018	0.0059
	T		109/113	103/105		.018	.017		.014	.011
Dibromo-chloro-methane	Q	47/111*	15/18	83/106	0.017*	0.013	0.0075	<0.0006-0.003[a]	.0019	.0021
	T		97/113	97/105		.014	.011		.0035	.0031
Tetra-chloro-methane	Q	3/111*		8/106	0.0029*		.0064	0.001-0.002[a]		<0.0002-0.0004[a]
	T		10/110	11/105		0.0024	0.0043		<0.0002[a]	<0.0002-0.0004[a]
Dichloro-methane		15/109			0.0061			<0.001-0.002[a]		

*Samples shipped iced, stored 1-2 weeks refrigerated before analyses.

[+] Quenched (Q) samples preserved with sodium thiosulfate at sampling, shipped at ambient temp., stored 20-25°C 3-6 weeks before analyses. Terminal(T) samples treated similarly to Q except no Na thiosulfate.

[a] Minimum quantifiable limits.

Phases (I, II, III) refer to sampling projects and corresponding sample treatment and storage conditions.
- I: Collected and analyzed as in National Organics Reconnaissance Survey (earlier) (Symons, et al. 1975). Shipped and stored refrigerated (1-8°C) 1-2 weeks before analyses.
- II: Samples stood at 20-25°C 3-6 weeks before analyses. Trihalomethanes (THM) formation proceeded to reaction endpoints (terminal values).
- III: Sampled with and without chlorine-reducing agent (quenched, terminal values) to assess effect of residual chlorine and reaction time.

Evidence of the presence of trichlorofluoromethane in ocean surface waters has been reported (Howard, et al. 1974; Lovelock, et al. 1973; Wilkness, et al. 1975). None was detectable below surface waters, indicating that the oceans are not a significant sink (long-term pool or repository) for this compound. As noted above, trichlorofluoromethane has been detected, but not quantified, in finished drinking water in the NOMS. Environmental data suggest that human exposure to the refrigerant-propellant chlorofluoromethanes in water is much less significant than to these compounds' presence in air.

Ingestion from Foods

Bromomethane residues from fumigation decrease rapidly through loss to the atmosphere and reaction with protein to form inorganic bromide residues. With proper aeration and product processing most residual bromomethane will rapidly disappear due to methylation reactions and volatilization. The more persistent inorganic bromide residues are products of bromomethane degradation (Natl. Acad. Sci., 1978; Davis, et al. 1977). Scudamore and Heuser (1970) reported that residues in fumigated wheat, flour, raisins, corn, sorghum, cottonseed meal, rice, and peanut meal were reduced to less than 1 mg/kg within a few days. Initial levels of inorganic bromide were positively related to concentration used, and disappearance rate was lower at low temperatures. No residual bromomethane was found in asparagus, avocados, peppers, or tomatoes after two-hour fumigation at 320 mg CH_3Br/m^3 air (Seo, et al. 1970). Only trace amounts were present in wheat flour and other products fumigated at 370 CH_3BR

mg/m^{3}after nine days of aeration (Dennis, et al. 1972).

Table 5 summarizes data on organic and inorganic bromide residues in cheese with time after fumigation, as reported by Roehm, et al. (1943). Table 6 summarizes specific inorganic bromide residue maxima analyzed in several food commodities, according to Getzendaner, et al. (1968). Lynn, et al. (1963) reported that cows fed grain fumigated with bromomethane gave milk containing bromide levels proportional to those in feed intake. Milk bromide levels of up to 20 mg/l were noted at exposure levels up to 43 mg inorganic bromide/kg diet, at which level milk production was not affected. Blood total bromides correlated with milk bromides.

TABLE 5

Bromomethane Residues in Cheese (outer ¼ inch) (mg/kg)
(Natl. Acad. Sci., 1978, data from Roehm, et al. 1943)

Hours of Ventilation	Longhorn Cheese A			Longhorn Cheese B		
	Inorganic	Organic	Total	Inorganic	Organic	Total
0.5	15	62	77	23	78	101
4	21	40	61	30	54	84
24	22	20	42	38	9	47
48	25	0	25	39	4	43
96	24	0	24	38	1	39
168	25	1	26	36	2	38

TABLE 6

Specific Residue Maxima: Inorganic Bromide in Food Materials (NAS, 1978, data from Getzendaner, et al. 1968)

Max. SR[a] $mg\text{-}kg^{-1}lb^{-1}min^{-1}$	Materials
0-5	Baking powder, butter, chewing gum, dry yeast, macaroni, marshmallows, oleomargarine, shortening, tapioca, flour, tea, whole roasted coffee
5-10	Cake mix, candy, cheese, dried milk, ground ginger, ground red pepper, pancake mix, precooked breakfast cereals, veal loaf
10-15	Cocoa, ground roasted coffee, powdered cinnamon
15-20	Allspice, beef cuts, gelatin, noodles, peanuts, pie crust mix
20-30	Cornmeal, cream of wheat, frankfurters, pork cuts, rice flour.
30-40	Bacon, dry dog food, mixed cattle feed, white and whole wheat flour
40-50	Soy flour
75-100	Grated Parmesan cheese
100-125	Powdered eggs

[a] Specific Residue (SR) $= \frac{\text{increase in bromide from fumigation(mg/kg)}}{\text{rate of fumigation (lb/min)}}$

Chloromethane and bromomethane are considered to have relatively low potentials for bioconcentration, judging from their relatively high vapor pressure and water solubility. Estimating from solubility and use of the Metcalf and Lu (1973) equation, biomagnification factors for these compounds are relatively low (two and six, respectively). No directly determined bioaccumulation factors were available.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the nineteen major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

No measured steady-state bioconcentration factor (BCF) is available for methylene chloride or bromoform but the equation "Log BCF = 0.76 Log P - 0.23" can be used (Veith, et al. Manuscript) to estimate the BCF for aquatic organisms that contain about eight percent lipids from the octanol-water partition coefficient (P). Based on an octanol-water partition coefficient of 18 for methylene chloride the steady-state bioconcentration factor for methylene chloride is estimated to be 5.2. The steady-state bioconcentration factor for bromoform is estimated to be 48, based on an octanol-water coefficient of 330. An adjustment factor of 2.3/8.0 = 0.2875 can be used to adjust the estimated BCF from the 8.0 percent lipids on which the equation is based to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for methylene chloride and the edible portion of all aquatic organisms consumed by Americans is calculated to be 5.2 x 0.2875 = 1.5. Similarly, for bromoform it is calculated to be 48 x 0.2875 = 14.

Inhalation

Reported concentrations of several halomethanes in general air masses are summarized in Table 7. For comparison, some halomethanes other than those addressed by this document (Table 1) are included.

Saltwater atmospheric background concentrations of chloromethane averaging about 0.0025 mg/m^3 have been reported (Grimsrud and Rasmussen, 1975; Singh, et al. 1977; Lovelock, et al. 1973). These are higher than reported average continental background and urban levels (ranging from 0.001 to 0.002 mg/m^3) and suggest that the oceans are a major source of global chloromethane (Natl. Acad. Sci., 1978). Localized

TABLE 7

Ranges of Mean Concentrations (mg/m^3) of Halomethanes Measured in General Air Masses

Compound	Continental Background	Saltwater Background	Urban
Chloromethane	0.0011-0.0021^{a,c,d,f,k}	0.0023; 0.0026^{d}	0.0017^{d}
Dichloromethane	0.0012^{c}	0.00012^{f}	(0.00007-0.0005)$^{+c}$
Bromomethane	0.00006^{d} (0.000002-0.000004)^{e}	0.00036^{d}	0.00042^{d} (0.00004-0.00085)^{e}
Iodomethane	0.000052^{d}	0.000041^{d} (0.000006-0.000064)^{i}	0.000139^{d} (0.000006-0.02204)^{g}
Trichloromethane	0.000044-0.000122^{a,c,d}	0.000132, 0.000234^{d}	0.000498 (0.000049-0.0732)^{g} (0.000029-0.01464)^{i}
Tetrachloromethane	0.000126-0.000838^{a,c,d,k}	0.000699-0.000806^{b,d,f}	0.000844^{d} (0.000756-0.1134)^{g} (0.00882)^{h} (0.000756-0.00945)^{i}

[+] Brackets identify individual reported values; other numerals represent reported means or range of reported means.

[a-l] Adapted from Natl. Acad. Sci., 1978, data from: (a) Cronn, et al. 1976; (b) Pierotti, et al. 1976; (c) Pierotti and Rasmussen, 1976; (d) Singh, et al. 1977; (e) Harsch and Rasmussen, 1977; (f) Cox, et al. 1976; (g) Lillian, et al. 1975; (h) Ohta, et al. 1976; (i) Su and Goldberg, 1976; (j) Lovelock, et al. 1973; (k) Grimsrud and Rasmussen, 1975; (l) Lovelock, 1975

sources, such as burning of tobacco or other combustion processes, may produce high indoor-air concentrations of chloromethane (up to 0.04 mg/m^3) (Natl. Acad. Sci., 1978, citing Palmer, 1976, and Harsch, 1977). Chloromethane is the predominant halomethane in indoor air, and is generally in concentrations two to ten times ambient background levels (Natl. Acad. Sci., 1978). Although direct anthropogenic sources of chloromethane greatly influence indoor atmosphere concentrations, they are not significant contributors to urban and background tropospheric levels (Natl. Acad. Sci., 1978).

Data on atmospheric bromomethane are few (Singh, et al. 1977; Grimsrud and Rasmussen, 1975). Its continental background concentrations of 7.8 x 10^{-5} mg/m^3 or less are much lower than saltwater background and urban air concentrations (Natl. Acad. Sci., 1978). Relatively high concentrations of bromo-methane reported in surface seawater suggest that oceans are a major source of the compound (Lovelock, et al: 1973; Lovelock, 1975), and this is supported by high concentrations in saltwater atmosphere (Singh, et al. 1977). There is evidence that combustion of gasoline containing ethylene dibromide (EDB, an additive) is also a significant source of environmental bromomethane, and this is corroborated by urban air concentrations at least as high as those in saltwater air masses (Natl. Acad. Sci., 1978, citing Harsch and Rasmussen, 1977, and Singh, et al. 1977). Table 7 summarizes reported levels of bromomethane in tropospheric air masses. Concentrations of up to 8.5 to 10^{-4} mg/m^3 may occur outdoors locally with light traffic as a result of exhaust containing bromomethane as a combustion breakdown product of EDB in leaded gasoline. Similarly, indoor air contaminated by exhaust from cars burning EDB-containing leaded gasoline can have elevated concentrations of bromomethane (Natl. Acad. Sci., 1978, citing Harsch and Rasmussen, 1977).

Data on concentrations of dichloromethane in tropospheric air masses are scarce. As shown in Table 7, reported background concentrations in both continental and saltwater atmospheres were about 1.2 x 10^{-4} mg/m^3, and urban air concentrations ranged from less than 7 x 10^{-5} to 5 x 10^{-4} mg/m^3 (Natl. Acad. Sci., 1978, citing Pierotti and Rasmussen, 1976, and Cox, et al. 1976). Concentrations of dichloromethane in indoor air typically exceed tropospheric background levels because of local sources of contamination such as the use of aerosol hair spray or solvents (Natl. Acad. Sci., 1978, citing Harsch, 1977). Air sampled from various indoor locations contained dichloromethane at concentrations ranging from a low of 2 x 10^{-4} mg/m^3 (in a laundromat washer) to high values of 2.5 mg/m^3 (automobile dealer display floor), 4.9 mg/m^3 (records and automotive section of discount store), and even 8.1 mg/m^3 (beauty parlor waiting area) (Natl. Acad. Sci., 1978, citing Harsch, 1977). Indoor air has 10 to 1,000 times more dichloromethane than is present in unpolluted tropospheric air, and sometimes dichloromethane is the predominant halomethane contaminant (Natl. Acad. Sci., 1978).

Data through 1974 indicate that dichlorodifluoromethane is produced and used considerably more than trichlorofluoromethane and the other major fluorocarbon refrigerants (Howard, et al. 1974). This production and use appears to be reflected in atmospheric analyses showing higher concentrations for dichlorodifluoromethane than for trichlorofluoromethane. Concentrations over urban areas are several times those over rural areas and over oceans. This probably reflects that the primary modes of entry to the environment, use of refrigerants and aerosols, are greater in industrialized and populated areas (Howard, et al. 1974). Atmospheric concentrations of trichlorofluoromethane are higher during stagnant air conditions and decrease upon displacement or dilution by clean air. Conversely, concentrations in offshore air masses increase when displaced by polluted air masses from industrialized urban areas (Howard, et al. 1974; U.S. EPA, 1976; Wilkness, et al. 1975; Lovelock, 1971, 1972). Average concentrations of trichlorofluoromethane (F-11) reported for urban atmospheres have ranged from 9×10^{-4} to 3×10^{-3} mg/m^3, and for ocean sites, from 2.2×10^{-4} to 5×10^{-4} mg/m^3. Mean urban concentrations for dichlorodifluoromethane (F-12) ranged from 3.5×10^{-3} to 2.9×10^{-2} mg/m^3, and an ocean atmosphere mean of 5.7×10^{-4} mg/m^3 was reported (Howard, et al. 1974; Hester, et al. 1974; Simmonds, et al. 1974; Su and Goldberg, 1976; Wilkness, et al. 1973, 1975; Lovelock, et al. 1973; Lovelock, 1974). Concentrations in air near fluorocarbon release sites may be many times the average city levels. F-11 concentrations of 1.3×10^{-4} to 2.4×10^{-4} mg/m^3, about 100 times the city average, were measured near a polyurethane plant using the material as a blowing agent; near a cosmetics plant where aerosol cans are filled, levels were three to four times typical city readings (Howard, et al. 1974; Hester, et al. 1974).

The F-11 and F-12 fluorocarbons are regarded as very stable and persistent in the environment and are without tropospheric or oceanic sinks. Tropospheric lifetimes of ten to more than 40 years have been asserted, and an atmospheric half-life of 15 to 30 years for F-11 has been calculated (Howard, et al. 1974; U.S. EPA, 1976; Howard and Hanchett, 1975; Lovelock, et al. 1973; Wilkness, et al. 1973; Krey, et al. 1976). Concern has developed that fluorocarbons in the troposphere will diffuse into the stratosphere and catalytically destroy stratospheric ozone, with possible health and meteorologic effects, globally.

Trichlorofluoromethane and dichlorodifluoromethane have been measured at highly varying levels indoors in homes. F-11 concentrations of 1.7 x 10^{-3} to 2.9 mg/m^3 have been reported (Hester, et al. 1974). Similar levels have been measured in public buildings. Indoor concentrations were generally higher than in outside air. In a beauty shop, where fluorocarbon-pressured cosmetic sprays were apt to be used, concentrations of 0.28 and 1.8 mg/m^3 were reported for F-11 and F-12, respectively. Evidence of quite high levels of propellants F-11 and F-12 after spray-product releases indoors was presented by Bridbord, et al. (1974 cited in U.S. EPA, 1976). These data are summarized in Table 8.

TABLE 8

Dichlorodifluoromethane Concentrations in Room Air as a Result of Release of Aerosol Can Products (U.S. EPA, 1976, data from Bridbord, et al. 1974)

Level at Periods after 60-second Release of Hair Spray in 29.3m^3 Room (mg/m^3)		Level at Periods after 30-second Release of Insect Spray in 21.4m^3 Room (mg/m^3)	
During:	306.8	1 min:	2,304.0
30 min:	12.4	60 min:	130.4
60 min:	0.5	150 min:	56.8

Data on environmental concentrations of halomethanes indicate that human uptake of the trihalomethanes bromodichloromethane and tribromomethane from fluids is less than that of trichloromethane. Uptake of chloromethane, dichloromethane, bromomethane and the chlorofluoromethanes from fluids is apparently minor; for these, uptake from sources other than fluid consumption is more important (Natl. Acad. Sci., 1978).

Human uptake of chloromethane from fluids should be considerably less than that for bromodichloromethane and triboromomethane. However, human exposure to chloromethane from cigarette smoke, local in nature and affecting discrete target populations, can be quite significant (Natl. Acad. Sci., 1978, citing Philippe and Hobbs, 1956, Owens and Rossano, 1969, and Chopra and Sherman, 1972). Reports or estimates of air concentrations in rooms with people smoking range roughly from 0.03 to 0.12 mg/m^3. The smoker's exposure from direct inhalation could be considerably greater still, since the range of reported chloromethane is 0.5 to 2 mg per cigarette.

Dermal

Uptake of halomethanes from dermal exposure can occur under certain circumstances. Occupational exposure standards warn of possible significant skin absorption for bromomethane and tribromomethane under industrial exposure conditions (Occup. Safety Health Admin., 1976; Natl. Acad. Sci., 1978). But there was no evidence in the available literature that dermal exposure contributes significantly to total dose of halomethanes for the general public.

PHARMACOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Most of the literature regarding biological aspects of the halomethanes has focused on the usual case with respect to exposure, absorption, and intoxication. Absorption via the lungs upon inhalation is of primary importance and is fairly efficient for the halomethanes; absorption can also occur via the skin and gastrointestinal (GI) tract, although this is generally more significant for the nonfluorinated halomethanes than for the fluorocarbons (Natl. Acad. Sci., 1978; Davis, et al. 1977; U.S. EPA, 1976; Howard, et al. 1974).

Bromomethane: The usual route for systemic poisoning by bromomethane is by inhalation, and absorption commonly occurs via the lungs; some absorption can also occur through the skin, particularly in skin exposures to the compound in liquid form (Davis, et al. 1977; von Oettingen, 1964).

Occupational Safety and Health Administration (1976) exposure standards warn of possible significant dermal absorption. Significant absorption can also occur via the gastrointestinal tract when bromomethane is ingested. Upon absorption, blood levels of residual nonvolatile bromide increase, indicating rapid uptake of bromomethane or its metabolites (Miller and Haggard, 1943). Bromomethane is rapidly distributed to various tissues and is broken down to inorganic bromide. Storage, only as bromides, occurs mainly in lipid-rich tissues.

Blood bromide levels of 24 to 250 mg/l were reported in severe, and 83 to 2,116 mg/l in fatal, bromomethane poisonings; normal background blood bromide levels ranged up to 15 mg/l (Natl. Acad. Sci., 1978, citing: Clarke, et al. 1945, Benatt and Courtney, 1948). In rats fed bromomethane-fumigated diets with residual bromide levels, higher tissue bromide levels were in their eyes, lungs, blood, spleen, and testes, while lowest tissue levels were in fat, skeletal muscle, bone, and liver. In similar bovine experiments, bromide was secreted in milk (Williford, et al. 1974; Lynn, et al. 1963).

Evidently the toxicity of bromomethane is mediated by the bromomethane molecule itself and its reaction with tissue (methylation of sulfhydryl groups in critical cellular proteins and enzymes), rather than by the bromide ion residue resulting from breakdown of the parent compound (Davis, et al. 1977). Bromomethane readily penetrates cell membranes while the bromide ion does not. Intracellular bromomethane reactions and decomposition result in inactivation of intracellular metabolic processes, disturbed function, and irritative, irreversible, or paralytic consequences (Natl. Acad. Sci., 1978; Davis, et al. 1977; Miller and Haggard, 1943; Lewis, 1948; Rathus and Landy, 1961; Dixon and Needham, 1946). Poisoning with bromomethane is generally associated with lower blood bromide levels than is poisoning with inorganic bromide (Natl. Acad. Sci., 1978, citing Collins, 1965).

Elimination of bromomethane is rapid initially, largely through the lungs as bromomethane. The kidneys eliminate much of the remainders as bromide in urine. Final elimination may take longer, accounting in part for prolonged toxicity (Natl. Acad. Sci., 1978 citing Miller and Haggard, 1943, and Clarke, et al. 1945).

Chloromethane: As with bromomethane, chloromethane is usually encountered as a gas and is absorbed readily via the lungs. Skin absorption is less significant (Natl. Acad. Sci., 1978; Davis, et al. 1977). No poisonings involving gastrointestinal absorption have been reported. Uptake of chloromethane by the blood is rapid but results in only moderate blood levels with continued exposure. Signs and pathology of intoxications suggest wide tissue (blood, nervous tissue, liver, and kidney) distribution of absorbed chloromethane. Initial disappearance from the blood occurs rapidly. Decomposition and sequestration result primarily by reaction with sulfhydryl groups in intracellular enzymes and proteins. Excretion via bile and urine occurs only to a minor degree (Natl. Acad. Sci., 1978; Davis, et al. 1977; Lewis, 1948; Morgan, et al. 1967; von Oettingen, 1964).

Dichloromethane: Absorption occurs mainly through the lung but also through the gastrointestinal tract and to some extent through intact skin. Lung absorption efficiencies of 31 to 75 percent have been reported, influenced by length of exposure, concentration, and activity level (Natl. Acad. Sci., 1978; Natl. Inst. Occup. Safety Health, 1976a, citing: Lehmann and Schmidt-Kehl, 1936, Riley, et al. 1966, DiVincenzo, et al. 1972, and Astrand, et al. 1975). Upon inhalation and absorption, dichloromethane levels increase rapidly in the blood to equilibrium levels that depend primarily upon atmosphere concentration; fairly uniform distribution to heart, liver, and brain is reported (Natl. Acad. Sci., 1978, citing von Oettingen, et al. 1949, 1950). Carlsson and Hultengren (1975) reported that dichloromethane and its metabolites were in highest concentrations in white adipose tissue, followed in descending order by levels in brain and liver. Dichloromethane is excreted intact primarily via the lungs, with some in the urine. DiVincenzo, et al. (1972) have reported that about 40 percent of absorbed dichloromethane undergoes some reaction and decomposition process in the body (Natl. Acad. Sci., 1978).

Some of the retained dichloromethane is metabolized to carbon monoxide (CO). Some of this CO is exhaled, but a significant amount is involved in the formation of carboxyhemoglobin (COHb). The formation of COHb leads to interference with normal oxygen transport capabilities of blood, so relative oxygen deprivation and secondary effects ensue (Natl. Inst. Occup. Safety Health, 1976a, citing Stewart, et al. 1972a, Fassett, 1978, and DiVincenzo and Hamilton, 1975; Natl. Acad. Sci., 1978, citing Stewart, et al. 1972a,b). Bioconversion of CO and formation of COHb continues after exposure. Therefore, cardiorespiratory stress from elevated COHb may be greater as a result of dichloromethane exposure than from exposure to CO alone (Stewart and Hake, 1976). Other metabolites of dichloromethane include carbon dioxide, formaldehyde, and formic acid (Natl. Acad. Sci., 1978).

Tribromomethane: Absorption occurs through the lungs upon inhalation of vapors, from the GI tract upon ingestion, and to some extent through the skin. The OSHA (1976) standard warns of possible significant skin absorption. Some of the body burden is biotransformed in the liver to inorganic bromide. After inhalation or rectal administration of tribromomethane bromides were found in tissues and urine (Natl. Acad. Sci., 1977). Bioconversion of tribromomethane and other trihalomethanes, apparently by a cytochrome P-450 dependent mixed function oxidase system, to carbon monoxide has been reported (Ahmed, et al. 1977). Excretion occurs partly through the lungs as tribromomethane, and complete excretion requires considerable time (Natl. Acad. Sci., 1978).

Bromodichloromethane: Little information is available on the pharmacokinetics or other biological aspects of this compound. This reflects its very limited use, primarily in research, and limited discharge to the environment (Natl. Acad. Sci., 1978). Current increased environmental interest in bromodichloromethane focuses on its presence in drinking water (Kleopfer, 1976) along with other trihalomethanes, as a consequence of chlorination. Absorption, distribution, metabolism, and excretion may resemble that of bromochloromethane (see the following) dichloromethane, or dibromomethane, in view of close chemical similarities among these compounds and bromodichloromethane. Further possible evidence for similarity exists in that the mutagenic, carcinogenic, and general toxic effects of the latter are similar to those of other di-and trihalogenated (Cl and Br) methanes (Natl. Acad. Sci., 1978; Sax, 1968).

Patty (1963) placed bromochloromethane "roughly in a class with methylene chloride," but "somewhat more toxic," among "the less toxic halomethanes." Animal experiments have indicated that inhaled bromochloromethane is readily absorbed intact by the blood and hydrolyzed in significant amounts by the body to yield inorganic bromide. Tissue concentrations of both organic and inorganic bromine increased in dogs and rats exposed daily to bromochloromethane. After exposure, blood levels decreased to undetectable or insignificant levels in 17 to 65 hours. Significant absorption by the GI tract after exposure by ingestion was indicated by hepatic and renal pathology in mice dosed by stomach tube. Similar injury in these organs was not observed in animals exposed to vapors. Absorption through the skin would also seem likely in view of its irritation and solubility characteristics (Patty, 1963).

If the pharmacokinetics of bromodichloromethane does resemble that of chemically similar halomethanes, it would be expected that bromodichloromethane would: (1) Be absorbed readily by the inhalation and ingestion routes; (2) be distributed widely, preferentially to tissues with high lipid content; (3) be eliminated in part via expired breath; and (4) combine with cellular protein and be metabolized to CO and inorganic halide.

Trichlorofluoromethane (F-11) and dichlorodifluoromethane (F-12): Inhalation and absorption through the lungs are the exposure and uptake modes of most concern; however, when ingested, absorption of F-12 does occur via the GI tract. Some absorption through the skin could occur also, judging from tests with F-113 ($CCl_2F-CClF_2$) (U.S. EPA, 1976; Howard, et al. 1974; Clark and Tinston, 1972a,b; Allen and Hanbury, 1971; Azar, et al. 1973; Sherman, 1974; DuPont, 1968). Absorption and elimination are dynamic processes involving equilibria among air, blood, and various tissues. Upon absorption a biphasic blood-level pattern occurs, with an initial rapid then slower rise in blood levels (arterial, venous) during which the material is absorbed from blood into tissues. After termination of exposure a similar but inverse biphasic pattern of elimination occurs. The relative decreasing order of several fluorocarbons with respect to absorption into blood has been reported as F-11, F-113, F-12, F-114 (Shargel and Koss, 1972; Morgan, et al. 1972). These authors agree in general with partition coefficients for the fluorocarbons in blood, serum, and lipid (oil) (Allen and Hanbury, 1971; Chiou and Niazi, 1973; Morgan, et al. 1972). More easily absorbed compounds are retained longer. Under conditions of prolonged, lower-level exposure, periods of elimination (washout) are longer. Although varying among individuals, apparently F-11 is more readily absorbed in mammals than F-12. To what extent this reflects artifacts involving the higher volatility of F-12 is not clear (Howard, et al. 1974).

F-11 and F-12 are distributed by blood and stored temporarily by various tissues. Measured tissue levels in rats after pulse inhalation exposure in one report were: adrenals greater than fat greater than heart (Allen and Hanbury, 1971). Chemically related fluorocarbons have been found primarily in tissues of high lipid content (fat, brain, liver, heart), but elimination following pulse exposure was rapid, and there was no evidence of accumulation (Carter, et al. 1970a,b; Van Stee and Back, 1971). There is evidence, however, that tissues with higher lipid content than blood concentrate fluorocarbons from the blood, corresponding to relative order of absorption by blood from air (Howard, et al. 1974).

Elimination of fluorocarbons (intact) seems to be almost completely through the respiratory tract, regardless of the route of entry. In dogs administered a mixture of F-12 and F-14 (30:70 percent, vol./vol.) by several different routes, elimination was through expired air and none was detected in urine or feces (Matsumoto, et al. 1968). Rapid initial elimination is followed by a slower phase of decline.

Biochemical effects suggesting a slowing down of cellular oxidation were reported in animals exposed to 2.8×10^5 mg/m^3 F-11 in air (but not to F-11 at 1.4×10^5 mg/m^3 nor to F-12 at 2.47×10^5 to 9.88×10^5 mg/m^3) (Paulet, et al. 1975).

In brief exposure experiments with inhaled ^{14}C-labeled F-12 only about one percent of F-12 was metabolized and eliminated in expired air as CO_2 or existed in nonvolatile urinary or tissue components (Blake and Mergner, 1974). Experiments with oral ^{14}C-labeled F-12 indicated that about two percent of the total dose was exhaled as CO_2, about 0.5 percent was excreted in urine, and after 30 hours no F-12 was detectable (Eddy and Griffith, 1961).

F-11 and F-12 form metabolites which bind to cell constituents, particularly in long-term exposures with extended equilibrium (Blake and Mergner, 1974). F-11 (or its labeled metabolites) has been reported to bind *in vitro* irreversibly to proteins and to endoplasmic phospholipids and proteins, but not to ribosomal RNA (Uehleke, et al. 1977; Uehleke and Warner, 1975). Binding to rat-liver microsomal cytochrome P-450-related phospholipids was reported (Cox, et al. 1972). More research on fluorocarbon xenobiotic metabolism and pharmacodynamics under prolonged exposure conditions is needed (U.S. EPA, 1976).

EFFECTS

Acute, Sub-acute, and Chronic Toxicity

For most of the halomethanes considered here, there is considerable information on clinical toxicity in the occupational health literature and on experimental toxicity in the literature on toxicology using laboratory animals. These data have dealt primarily with inhalation exposure to grossly poisonous or fairly substantial concentrations of vapors. Considerably less information is available on various aspects of toxicity that might result from prolonged exposure to low, environmental levels of these contaminants, by not only the inhalation route but also ingestion or other routes of exposure. This section summarizes briefly the important clinical and toxicologic information available for these compounds.

Chloromethane: Is not generally regarded as highly toxic, yet reports of poisoning are numerous. Because of its virtually odorless and colorless properties, low-order irritancy,and characteristic latency of effect, victims may receive serious or prolonged exposure before awareness and effects are apparent (Natl. Acad. Sci., 1978; Davis, et al. 1977). Toxic dosages for humans are not clearly defined. Generally, acute inhalation intoxication in humans has been thought to require exposures on the order of 1,032 mg/m^3, but lower levels have produced definite toxicity in animals (MacDonald, 1964; Smith and von Oettingen, 1947b,c). Chronic inhalation and ingestion toxicity levels are not established, but the occupational exposure standard for air in the work environment is currently set for 206 mg/m^3 (Natl. Acad. Sci. 1978; Occup. Safety Health Admin., 1976). The monohalomethanes seem to rank in the following order of decreasing toxicity: iodomethane, bromomethane, chloromethane, fluoromethane (Davis, et al. 1977). The similarities in toxicologic responses to the monohalomethanes suggest a similar mode of action. The most probable mechanism is that the monohalomethane participates in the methylation of essential enzymes, cofactors, and other cellular macromolecules, thereby rendering them inactive (Davis, et al.

1977). Sulfhydryl-containing molecules seem particularly susceptible to the action of monohalomethanes (Lewis, 1948; Redford-Ellis and Gowenlock, 1971a). Various reports on the effectiveness of cysteine administration in the treatment of monohalomethane poisoning support the contention that binding to sulfhydryl compounds is involved in the expression of toxic effects (Mizyokova and Bakhishev, 1971). In studies with laboratory animals, several investigators have shown that monohalomethanes interfere with glutathione metabolism (Redford-Ellis and Gowenlock, 1971a,b; Boyland, et al. 1961; Barnsley, 1964; Johnson, 1966; Barnsley and Young, 1965).

Human experience, largely involving leakage from refrigeration equipment using chloromethane as a coolant, shows it to be a central nervous system (CNS) depressant with primarily neurological toxic manifestations (Hansen, et al. 1953). Systemic poisoning cases have also involved hepatic and renal injury (Spevac, et al. 1976). In the more mild intoxications there is a characteristic latent period of one-half to several hours between exposure and onset of effects (symptoms). Recovery after brief exposures is typically within a few hours, but repeated or prolonged exposure may result in more severe toxicity and delayed recovery (days-weeks). In persons occupationally exposed at levels of 52 to more than 2 x 10^4 mg/m^3 the following toxic manifestations, particularly related to CNS, were noted: blurred vision, headache, nausea, loss of coordination, personality changes (depression, moroseness, anxiety), lasting a few hours to several days; some were more sensitive to chloromethane upon return to work (MacDonald, 1964; Hansen, et al. 1953; Browning, 1965; Morgan, 1942). As mentioned previously, tobacco-smoking may be an additional significant source of individual human exposure to chloromethane.

Severe poisonings are usually characterized by a latent period and severe and dominant neurological disorder, with perhaps irreversible and/or persistent sequelae; renal and hepatic injury are common. In fatal cases coma and death commonly ensue in hours or days as a result of cerebral and pulmonary edema and circulatory failure, with pathologic findings of congestion, edema, and hemorrhage; chloromethane has been detected in all organs analyzed after death (Natl. Acad. Sci., 1978, citing Baird, 1954).

There have been no reports of reproductive toxicity or teratogenicity in humans exposed to chloromethane, but metabolic, enzymatic, and neuroendocrine disturbances following exposure in humans and/or animals suggest the need for research on this point (Davis, et al. 1977). Epidemiological studies of toxicity in human populations exposed to chloromethane (including mutagenicity and carcinogenicity) have not yet appeared in the published literature.

In animals, a variety of toxic effects have been noted in experimentally exposed subjects. Many effects are similar for the monohalomethanes and, consistent with human data, suggest CNS involvement and altered metabolism involving binding to sulfhydryl-containing cellular macromolecules (Davis, et al. 1977; Balander and Polyak, 1962; Gorbachev, et al. 1962; Kakizaki, 1967; Redford-Ellis and Gowenlock, 1971a,b). Most toxicity information is from inhalation studies, with little regarding other routes, apparently because of the volatility of these compounds and their usual presence in the gas phase (Davis, et al. 1977). Some inhalation toxicity data for chloromethane are summarized in Table 9. In general, chloromethane appears less acutely toxic by inhalation than bromomethane. In severe acute exposure conditions chloromethane produces serious neurological disturbances, with functional and behavioral manifestations and ultimately death. However, these disturbances from chloromethane occur at higher concentrations than are required for bromomethane in several species (Davis, et al. 1977).

Under more prolonged exposures to less severe levels, chloromethane increased mucus flow and reduced mucostatic effect of other agents (e.g., nitrogen oxides) in cats (Weissbecker, et al. 1971). Permanent muscular dysfunction is described in mice surviving several weeks of daily exposures at 1,032 mg/m^3, and paralysis followed exposure to 531 mg/m^3 for 20 hours in surviving animals (von Oettingen, et al. 1964). No teratogenic effects have been reported for chloromethane (Davis, et al. 1977).

Bromomethane: is regarded as a highly toxic substance by acute exposure and more dangerous than chloromethane. It has been responsible for many occupational poisoning incidents, reflecting its widespread use as a fumigant. Like chloromethane it has a characteristic latent period and its presence is difficult to detect, so prolonged and

TABLE 9

Chloromethane Inhalation Toxicity in Animals

Concentration, mg/m^3	Duration	Response	Reference
3.1×10^5 to 6.2×10^5	Brief	Quickly lethal to most animals	Patty, 1958
4.1×10^4 to 8.3×10^4	30-60 min	Dangerous effects. Increased respiratory and heart rates and blood pressure, followed by reversals and ECG changes; restlessness, salivation, incoordination, narcosis.	von Oettingen, 1964
4.1×10^4	2 hr.	LCLo, guinea pig	NIOSH, 1976b
1.4×10^4	Up to 1 hr	No serious effects	Patty, 1958
6.2×10^3 to 8.3×10^3	6 hrs/day	Deaths, rats, 3-5 days, spasmodic dyspnea	von Oettingen, 1964
6.5×10^3	6 hrs	LC_{50}, mouse	Davis, et al. 1977
6.2×10^3	4 hrs	LCLo, rat	DHEW, 1975
4.1×10^3	6 hrs/day	1 week, cats, weakness, unable to right 1 week, cats, dyspnea, refusal to eat/drink. 3-4 weeks, cats, death 2-3 days, guinea pigs, deaths 4-7 days, monkeys, convulsions 1-3 days, dogs, deaths 5-6 days, rabbits and rats, death 1-6 days, dogs, deaths	von Oettingen, 1964
2,065	6 hrs/day	1 expos., dogs and monkeys, signs of poisoning; 2-4 weeks, dogs, deaths, permanent neuromuscular damage in survivor;	von Oettingen, 1964
1,032	6 hrs/day	1 week, mice, convulsions, mortality; 15 weeks, mice, permanent adductor contraction in survivors	von Oettingen, 1964
620 to 1,032		Overt signs of toxicity detectable in dogs and monkeys.	Smith & von Oettingen, 1947a
531	20 hrs	Paralysis in survivors (but in another exposure at 620 mg/m^3, no cumulative overt toxicity or neurotoxic changes over several months in several species).	von Oettingen, 1964; Smith & von Oettingen, 1947a

more severe exposure may be incurred (Natl. Acad. Sci., 1978; Davis, et al. 1977). Toxicologic and metabolic similarities among the monohalomethanes (Cl-, Br-, I-substituted) suggest a common mechanism of toxic action, probably methylation and disturbance or inactivation of essential proteins (rather than presence of the parent compound or free halide per se) (Davis, et al. 1977).

Human experience indicates that acute fatal intoxication can result from exposures to vapor levels as low as 1,164 to 1,552 mg/m^3, and harmful effects can occur at 388 mg/m^3 or more. Systemic poisoning has been reported to occur from two weeks' exposure (eight hrs/day) at about 136 mg/m^3 (Natl. Acad. Sci., 1978, citing: Kubota, 1955, Johnstone, 1945, Bruhin, 1943, Wyers, 1945, Watrous, 1942, Rathus and Landy, 1961, Miller, 1943, Tourangeau and Plamondon, 1945, Viner, 1945, Collins, 1965, Clarke, et al. 1945). Symptoms generally increase in severity with increasing levels of exposure and may vary somewhat according to exposure circumstances and individual susceptibility. In sublethal poisoning cases a latency period of 2 to 48 hours (usually about four to six) between exposure and onset of symptoms is characteristic (Araki, et al. 1971).

Like the other monohalomethanes, bromomethane is a CNS depressant and may invoke psychic, motor, and GI disturbances. (Mellerio, et al. 1973, 1974; Greenberg, 1971; Longley and Jones, 1965; Hine, 1969). In light poisoning cases effects may be limited to mild neurological and GI disturbances, with recovery in a few days. Moderate cases involve the CNS further, with more extensive neurological symptoms and visual disturbances. Recovery may be prolonged for weeks or months, with persisting symptoms and/or disturbed function. Severe cases also involve a latent period and similar initial symptoms, with development of disturbed speech and gait, incoordination, tremors that may develop to convulsions, and psychic disturbances. Recovery can be quite protracted with persisting neurological disorders (Araki, et al. 1971). In fatal cases the convulsions may become more intense and frequent, with unconscious periods. Death may occur in a few hours from pulmonary edema or in one to three days from circulatory failure. Pathology often includes hyperemia, edema, and inflammation in lungs and brain. Degenerative changes in kidney, liver, and/or stomach, and perhaps the brain, occur although brain changes are usually more functional in character (Natl. Acad. Sci., 1978; Davis, et al. 1977). Apparently blood bromide levels of 100 mg/l or less result in recovery, 135 in moderate disability, 195 in residual ataxia, and 250 in convulsions (Hine, 1969).

Direct skin contact with bromomethane may produce prickling, itching, cold sensation, erythema, vesication, blisters (similar to second degree burn), and damage to peripheral nerve tissue or delayed dermatitis (Davis, et al. 1977). A case of brief skin exposure (spray) to liquid bromomethane, quickly decontaminated, did not produce a burn, but resulted in severe, delayed, neuromuscular disturbances (twitching, fits, convulsions) and permanent brain damage (cerebellum and pyramidal tract) (Longley and Jones, 1965). The OSHA

(1976) standard for bromomethane in workroom air is 78 mg/m^3 (ceiling) and carries a warning notation of possible significant skin absorption (Natl. Inst. Occup. Safety Health, 1976b; Occup. Safety Health Admin., 1976).

In animals bromomethane is highly toxic. It is more toxic by inhalation to several species than chloromethane (Davis, et al. 1977). Correspondence between effective doses by inhalation vs. ingestion is difficult to assess until more is known of GI absorption and first-pass detoxification (Davis, et al. 1977). In several species acute fatal poisoning has involved marked CNS disturbances with a variety of manifestations: ataxia, twitching, convulsions, coma, as well as changes in lung, liver, heart, and kidney tissues (Sayer, et al. 1930; Irish, et al. 1940; Gorbachev, et al. 1962; von Oettingen, 1964). In subacute and protracted exposure studies similar neurological disturbances developed (Irish, et al. 1940; Sokolova, 1972) as in animal and human (Drawneek, et al. 1964) acute toxicoses. Inhalation toxicity in animal species is briefly reviewed in Table 10. In general the monohalomethanes rank in decreasing order of acute toxicity as follows: iodomethane, bromomethane, chloromethane, fluoromethane (Davis, et al. 1977).

Dogs receiving bromomethane chronically by ingestion (fumigated diet yielding residual bromide at a dose level of 150 mg/kg/day) were adversely affected, whereas if they received sodium bromide at 78 mg/kg/day (residual bromide) no effects were noted (Rosenblum, et al. 1960). In another experiment using fumigated food with residual bromide Vitte,

TABLE 10

Bromomethane Inhalation Toxicity in Animals

Concentration mg/m^3	Duration	Response	Reference
69,452	15 min	Lethal, cats	von Oettingen, 1964
24,929	1 hr	LCLo, rabbit	NIOSH, 1976b
20,952	20 min	Delayed deaths (6 days), guinea pigs	von Oettingen, 1964
7,760-11,640	30 min	Delayed deaths (9 hr), 1 of 6 guinea pigs	von Oettingen, 1964
7,760-11,640	70 min	LC_{100}, guinea pigs	von Oettingen, 1964
3,391	30-40 min	Lethal, dogs	von Oettingen, 1964
1,940-2,328	4.5 hrs	Lethal within 2 days, salivation, guinea pigs	von Oettingen, 1964
2,293	12 hrs	Lethal, rabbits	Gorbachev, et al. 1962
1,536-1,940	6 hr/daily	Cumulative overt toxicity, dogs & monkeys	Smith & von Oettingen, 1947a
1,536	Not specified	LC_{50}, mice	Balander & Polyak, 1962
1,164	5 hrs	Delayed death, 1 of 6 guinea pigs	von Oettingen, 1964
1,164	13.5 hrs	Lethal, all died within 3 days, guinea pigs	von Oettingen, 1964
997	22 hrs	100% lethal in rats	Irish, et al. 1940
846	3 hr	Lethal, rabbits	von Oettingen, 1964
846	26 hr	Lethal, rats	Irish, et al. 1940
582	9 hrs	Lethal to most in 1-3 days; guinea pigs	von Oettingen, 1964
504	18 hrs (2 exp. at 3 mo interval)	Altered conditioned reflexes, mice	Sokolova, 1972
419	7-8 hrs daily	Weight loss, prostration, convulsions; rats	Irish, et al. 1940
252	8 hr/day, 5 da/wk.	At 22 days: typical poisoning, rabbits	Irish, et al. 1941
128	8 hr/day, 5 da/wk.	Eventually lung irrit., paralysis, rabbits (but not rats, guinea pigs, or monkeys)	Irish, et al. 1941
97	4-5 mos	Altered neuroendocrine controlled metabolism, rabbits	Balander & Polyak, 1962
70	40 min	Changes in motor responses	Balander & Polyak, 1962

et al. (1970) detected changes in blood iodine and calcium and pathologic changes in thyroid and parathyroid glands. Toxic responses in rabbits administered bromomethane subcutaneously (in oil) at 20-120 mg/kg included limb paralysis, cessation of drinking, reduced urine excretion. Levels greater than 50 mg/kg sharply increased the blood bromide level and reduced platelets, serotonin, and water content (Kakizaki, 1967).

Groups of cattle were fed oat hay from a bromomethane-fumigated field or pelleted ration containing sodium bromide added at various concentrations. The hay contained bromide ion at 6,800 to 8,400 mg/l. Groups fed the hay and highest dose-rate of bromide in pelleted ration developed signs of CNS toxicity (motor incoordination) at 10 to 12 days of exposure. Incoordination correlated with serum bromide concentrations of 2,400 mg/l (30 meq/l) or more. Serum bromide levels and neurologic signs were markedly reduced two weeks after termination of exposure (Knight and Reina-Guerra, 1977).

No reports of bromomethane teratogenicity studies were available, but high levels in eye and testes after ingestion of fumigated food, and enzymatic and neuroendocrine disturbances, could have teratogenic implications. Further studies in this area would appear to be warranted (Williford, et al. 1974).

Dichloromethane: As with chloromethane, dichloromethane has not generally been regarded as highly toxic, but poisonings, primarily from inhalation exposures, have been reported. Human minimal toxic concentrations or doses have not been determined. At this time the OSHA occupational exposure standard (air concentrations as a TWA for eight hours) is 1,737 mg/m^3 with ceiling and peak values of 3,474 and 6,948 mg/m^3, respectively (Occup. Safety Health Admin., 1976). However, NIOSH has recommended an eight-hour TWA concentration of 260 mg/m^3 with a peak limit of 1,737 mg/m^3 (Natl. Inst. Occup. Safety Health, 1976b). A TCLo* (eight hours) of 1,737 mg/m^3 for humans is reported (Natl. Inst. Occup. Safety Health, 1976b), and exposures of 740 or 1,786 mg/m^3 for one hour were reported as being without adverse effect by Stewart, et al. (1972a,b). However, Winneke (1974) reported exposure to 1,101 mg/m^3 or more for three to four hours decreased psychomotor performance (Natl. Acad. Sci., 1978). Dichloromethane affects central nervous system function. It is also irritating to mucous membranes (eyes, respiratory tract) and skin. In addition, it results in production of carbon monoxide (CO) as a metabolite, which increases carboxyhemoglobin (COHb) in the blood and interferes with oxygen transfer and transport (Natl. Acad. Sci., 1978).

Mild poisonings by dichloromethane produce somnolence, lassitude, anorexia, and mild lightheadedness, followed by rapid and complete recovery. Severe cases are characterized by greater degrees of disturbed CNS function and depression. Permanent disability has not been reported. In fatal poisonings cause of death has been reported as cardiac injury and heart failure (Natl. Acad. Sci., 1978, citing: Hughes,

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*Abbreviation used to denote lowest reported toxic concentration.

1954, Stewart and Hake, 1976, Collier, 1936, Moskowitz and Shapiro, 1952).

The formation of CO and COHb from dichloromethane forms a basis for concern about combined exposures to dichloromethane and carbon monoxide. Fodor and Roscovanu (1976) and NIOSH (1976a) recommend re-examination of dichloromethane exposure standards with a view to reducing them. These authors report that exposure at the current threshold limit value (TLV) of dichloromethane produces COHb levels equivalent to those produced by the TLV for CO. Mixed exposures could be a problem, especially in workers, smokers, and cardiorespiratory patients or other susceptibles. Concern about mixed exposure to dichloromethane and other lipophilic solvents, with enhanced danger of marked CNS and metabolic effects resulting from modest exposure to individual materials, has been expressed (Savolainen, et al. 1977).

Gynecologic problems in female workers exposed for long periods to gasoline and dichloromethane vapors were reported by Vozovaya (1974). In pregnant women, chronic exposure resulted in dichloromethane passing through the placenta into the fetus. Dichloromethane also was found in milk of lactating women a few hours into a work shift. Functional circulatory disorders in workers exposed for more than three years to organochlorine compounds (including dichloromethane) at "permissible" levels have been reported by Dunavskii (1972). Symptoms included chest pain, electrocardiograph irregularities, bradycardia, decreased myocardial contractility, and altered adaption to physical stress.

More recently it has been reported (Stewart and Hake, 1976; Scott, 1976) that fatal heart attacks have been caused by exposure to dichloromethane in paint and varnish removers (Natl. Acad. Sci., 1978).

Animal toxicology of dichloromethane is briefly reviewed in Table 11, with some human data included. Both di- and tri-halogenated methane derivatives have been found to produce increased blood levels of COHb; the greatest increase caused by iodo-, followed by bromo- and chloro- compounds. CNS functional disturbances are reported, including depression of REM-sleep, as seen in carbon monoxide exposures (Fodor and Roscovanu, 1976). Liver pathology has been reported in experimental exposure to dichloromethane vapors (Balmer, et al. 1976). NAS (1978) cites Haun, et al. (1972) reporting liver changes in mice continuously exposed to dichloromethane at 87 and 347 mg/m^3 for up to two weeks. As a liquid or vapor dichloromethane was ophthalmotoxic in rabbit tests, producing persistent (up to two weeks) conjunctivitis and blepharitis, corneal thickening, keratitis and iritis, and increased intraocular tension (Ballantyne, et al. 1976). Inhalation exposures of rats and mice to vapor levels of 4,342 mg/m^3 for seven hours daily on gestation days 6 to 15 produced increased blood levels of COHb and evidence of feto - or embryo-toxicity, but not teratogenicity (Schwetz, et al. 1975; Natl. Inst. Occup. Safety Health, 1976a, citing Heppel and Neal, 1944).

At 1.737 mg/m^3 voluntary running activity was depressed in rats. Sleep alterations were noted in rats exposed to

TABLE 11

Toxicity of Dichloromethane

Exposure Concentration or Dose	Duration	Response	Reference
6,460 mg/kg	Subcut.	LD_{50}, mouse	NIOSH, 1976b
17,370 mg/m^3	2 hrs	LCLo, guinea pig. Depressed running activity, rats	NIOSH, 1976b Heppel & Neal, 1944*
3,000 mg/kg	Oral	LDLo, dog	NIOSH, 1976b
2,700 mg/kg	Subcut.	LDLo, rabbit and dog	NIOSH, 1976b
2,136 mg/kg	Oral	LD_{50}, rat	NIOSH, 1976b
1,900 mg/kg	Oral	LDLo, rabbit	NIOSH, 1976b
1,500 mg/kg	I.P.	LD_{50}, mouse	NIOSH, 1976b
4,342 mg/m^3	7 hr/day, 9 da	Fetotox., teratogenicity, mice, rats	Schwetz, et al. 1975$^+$
3,425 mg/m^3	1 hr	Transient lightheadedness, human	Stewart, et al. 1972a,b$^+$
950 mg/kg	I.P.	LDLo, dog	NIOSH, 1976b
1,737 mg/m^3	6 hr/day, few days	Altered brain metabolism, behavior, rats	Savolainen, et al. 1977
1,737 mg/m^3	year, intermittent	TCLo, CSN, human	NIOSH, 1976b
1,737 mg/m^3	8 hrs	TCLo, blood, human (12% COHb)	NIOSH, 1976b
1,737 mg/m^3	3 hrs	13% COHb, rats	Fodor & Roscovanu, 1976
200 mg/kg	I.V.	LDLo, dog	NIOSH, 1976b
87-347 mg/m^3	Contin. up to 2 wks.	Liver changes, mice	Haun, et al. 1972$^+$

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*Cited by NIOSH, 1976a

+Cited by NAS, 1978

dichloromethane at 3,474 mg/m^3 or more (Wolburg, 1973). Depressed CNS excitability, along with increased blood levels and expiratory, hepatic, and renal excretion of dichloromethane in subacute studies, was reported (Avilova, et al. 1973).

Tribromomethane: Little information is available concerning the toxicology of tribromomethane. It is regarded as a highly toxic material, more toxic than dibromomethane but less than tetrabromomethane and triiodomethane (Natl. Acad. Sci., 1978, citing Dep. Health Edu. Welfare, 1975). Minimum toxic concentrations have not been established, but its general toxic potential is reflected in a quite low occupational exposure standard (Occup. Safety Health Admin., 1976): eight-hour time-weighted-average air concentration, 5.2 mg/m^3 (the most stringent standard of the halomethanes considered herein). It is absorbed by all major routes (lungs, GI tract, skin) after appropriate exposure (Natl. Acad. Sci., 1978).

In humans, exposure to toxic levels of vapor produces irritation of respiratory tract, pharynx, and larynx, with lacrimation and salivation. Most reported cases of poisonings have resulted from accidental overdoses administered in the treatment of whooping cough. Toxic symptoms appear after a shorter latent period than that typical of other halomethanes. Obvious toxic effects in light cases may be limited to headache, listlessness, and vertigo. Unconsciousness, loss of reflexes, and convulsions occur in severe cases, and in fatal cases the primary cause of death is respiratory failure. Clinical recovery in moderate poisonings may be relatively rapid and without permanent damage or disabiltiy. Presence of tribromomethane in all organs is indicated by pathologic findings, which also indicate fatty degenerative and centralobular necrotic changes in the liver (as in trichloro - and triiodomethane poisonings) (Natl. Acad. Sci., 1978, citing von Oettingen, 1955).

Animal data are generally consistent with those from human case histories. Impaired liver function (prolonged pentobarbital sleeping time and/or BSP retention) in mice resulted from single subcutaneous doses of tribromomethane ranging between 278 and 1,112 mg/kg. These functional effects correlated with pathological liver changes at the higher dose levels (Kutob and Plaa, 1962). Pathological changes in liver and kidney have been reported (Dykan, 1962) in guinea pigs after systemic administration of a level of 100 to 200 mg/kg per day for ten days (Natl. Acad. Sci., 1978). Experimental data for animals are briefly summarized in Table 12. Reticuloendothelial system function (liver and spleen phagocytic uptake of ^{125}I-Listeria monocytogenes) was suppressed in mice exposed 90 days to tribromomethane at daily dose levels of 125 mg/kg or less (Munson, et al. 1977, 1978).

Bromodichloromethane: No information on human intoxication by this compound was available and there have been no occupational exposures reported by Sax (1968). However, he reported the compound as "dangerous" and "probably narcotic in high concentrations."

TABLE 12

Bromoform Toxicity in Animals

Concentration or Dose	Duration or Route	Response	Reference
1,820 mg/kg	Subcut., single	LD_{50}, mouse	Kutob & Plaa, 1962
1,400 mg/kg	Intragastric, single	LD_{50}, mouse, ICR, O; fatty liver; kidney palor; hemorrhage in adrenals, lungs, brain	Bowman, et al. 1978
581 mg/kg	Subacut., oil, single	Median effective dose for prolongation of phenobarb. sleeping time. Approx. thresh. 278 mg/kg. Mouse.	Kutob & Plaa, 1962
410 mg/kg	Subacut., single	LDLo, rabbit	NIOSH, 1976b
250 mg/m^3	Inhal., 4 hrs daily, 2 mos.	Disorders in liver glycogenesis and prothrombin synthesis; reduced renal filtration capacity. Threshold: 50 mg/m^3. Rat.	NAS, 1977, citing Dykan, 1962
100-200 mg/kg/da	Inject., daily, 10 days	Liver and kidney pathol., guinea pig	NAS, 1978, citing Dykan, 1962
0.3-125 mg/kg/da	Intragastric, 90 days	Suppressed liver phagocytosis, mice	Munson, et al. 1978

Bowman, et al. (1978) have recently reported on acute toxicity tests in mice. Median lethal doses LD_{50} for ICR Swiss mice administered bromodichloromethane (solubilized in emulphor: alcohol and saline mix) by gavage were 450 and 900 mg/kg for males and females, respectively. Based on comparative LD_{50} data among four trihalomethanes bromodichloromethane was the most acutely toxic in both males and females, and males were more susceptible than females for all compounds. Sedation and anesthesia occurred within 30 minutes at the 500 mg/kg dose level for bromodichloromethane, and lasted for about four hours. Animals that died in groups dosed over a range of 500 to 4,000 mg/kg showed fatty infiltration in livers, pale kidneys, and hemorrhage in kidneys, adrenals, lungs, and brain.

In mice that were offered bromodichloromethane in drinking water at 300 mg/l (with and without use of emulphor), water consumption and body-weight decreased dramatically (Campbell, 1978). Body weight regained parity with controls in several weeks, but water consumption did not. There was no obvious effect on susceptibility to pathogenic *Salmonella typhimurium* delivered by gavage after several weeks' exposure. However, Schuller, et al. (1978) have observed a suppression of cellular and humoral immune response indices in female ICR mice exposed by gavage for 90 days to bromodichloromethane at 125 mg/kg daily. Sanders, et al. (1977) observed hepatomegaly and a depression in a reticuloendothelial system functional index (phagocytic) in mice exposed to bromodichloromethane. Munson, et al. (1977) reported a dose-dependent suppression of hepatic phagocytosis in mice exposed for 90 days to daily doses of bromodichloromethane by gavage ranging up to 125 mg/kg.

Teratogenic properties of bromodichloromethane have not been clearly demonstrated, but some fetal anomalies were reported in experiments in which mice were exposed to vapors at 8,375 mg/m^3 seven hrs/day during gestation days 6 to 15 (Schwetz, et al. 1975).

Trichlorofluoromethane (F-11) and dichlorodifluoromethane (F-12): These propellant fluorocarbons are discussed together because of their physicochemical and general toxicologic similarity. They may be regarded as the least toxic of the halomethanes considered in this document. Standards for maximum average concentrations in air of work spaces are established at 5,600 and 4,950 mg/m^3 for F-11 and F-12, respectively (Occup. Safety Health Admin., 1976). For reference, these may be compared to the following standards for other halomethanes:

tribromomethane	5 mg/m^3
bromomethane	80 mg/m^3
chloromethane	206 mg/m^3
dichloromethane	1,737 mg/m^3

It has been recommended that these standards be reduced to 260 mg/m^3.

Because of their physical properties and use patterns the primary route of exposure in toxicity studies has been by inhalation of vapors at high concentrations, resulting in rapid pulmonary absorption. The two toxicologic features of the fluorocarbons that have received the greatest attention are their cardiovascular and bronchopulmonary actions. The toxicities of F-11 and F-12 are thought to be mediated at least in part by metabolic products which bind to lipid and protein cell constituents and affect vital processes (e.g., retard cellular oxidation). There remains a need for more metabolic and toxicologic information on the consequences of prolonged exposure to environmental levels (U.S. EPA, 1976; Howard, et al. 1974).

Human experience in fluorocarbon toxicity has largely involved the intentional or unintentional misuse of fluorocarbon products, resulting in acute inhalation of high vapor concentrations. Numerous severe and fatal cases of abuse are on record, such as from inhaling deeply from spray-filled bags to achieve a "jag." These probably involve cardiac arrhythmia complicated by elevated circulating catecholamines and CO_2 (Bass, 1970; Killen and Harris, 1972). Similar toxic consequences could occur in asthmatics using fluorocarbon-propellant bronchodilator products (Taylor and Harris, 1970; Archer, 1973). Occupational-exposure data are limited. Speizer, et al. (1975) have reported a relationship between cardiac palpitation episodes and level of use of F-12 and F-22* propellants in hospital pathology department workers (frozen-section preparation).

*F-22 is $CHCIF_2$

In brief experimental exposures of humans to F-12 at 198 x 10^3 mg/m^3 vapor concentration in air, tingling sensation, humming in the ears, apprehension, EEG and speech changes, and deficits in psychological performance were reported. In other tests exposures to F-12 at 49 x 10^3 to 543 x 10^3 mg/m^3 caused cardiac arrhythmia, decreased consciousness, and amnesia or deficits in performance on psychomotor tests scores (Kehoe, 1943; Azar, et al. 1972). However, in women using fluorocarbon-propellant (F-11, F-12, F-114*) aerosol products and receiving nine or more times the exposure from normal use, Marier, et al. (1973) found no measurable blood levels of the fluorocarbons or abnormalities in overall health, respiratory, or hematologic parameters.

Good, et al. (1975) reported an excess of atypical metaplastic cells in sputum of frequent aerosol-product users. The authors suggested the possibility of some products altering the resident bacterial flora of the respiratory tract or containing tumorigenic constituents (not necessarily the propellants). Data from a survey of aerosol product use and respiratory symptoms by Lebowitz (1976) led him to suggest a "tendency for more symptoms to follow increased aerosol usage, most consistently among non-smokers" (U.S. EPA, 1976). Human data on halothane** suggest potential toxic hazards (liver, kidney, and CNS changes; risk of abortion and developmental anomalies, increased susceptibiltiy to cancer in females) from prolonged exposure at relatively low levels, with implications particularly for operating room personnel. Animal data on halothane are generally supportive (U.S. EPA, 1976). The primary human hazard from F-11 inhalation (by whatever circumstance: intentional misuse of aerosol products to achieve intoxication or overuse of propellant bronchodilators) is the induction of cardiac arrhythmias (Howard, et al. 1974).

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*F-114 is $CClF_2$-$CClF_2$

*Halothane is a gaseous anesthetic and chemical cousin, CF_3-CHBrCl.

The inhalation toxicology of F-11 and F-12 in animals is selectively summarized in Tables 13, 14, and 15. Several propellant substances have been classified according to their cardiopulmonary toxicities in animal studies, as summarized in Table 16. Of all the aerosol propellants studied and classified on the basis of cardiopulmonary effects, Aviado (1975a) concluded that F-11 is the most toxic and that the most serious effects are induction of cardiac arrhythmia and sensitization to epinephrine-induced arrhythmias. The Underwriters Laboratories (1971) classification system for refrigerants is shown in Table 17. In this system F-11 and F-12 are in Toxicity Classes 5 and 6, respectively (the lowest two of six classes).

TABLE 13

Inhalation Toxicology of F-11 (U.S. EPA, 1976)

Concentration of Vapor (mg x $10^3/m^3$)	Exposure, Duration or Regimen	Subject	Effect(s)
1,851	Brief (N.S.)	Rat	Tremors
1,402	30 min	Rabbit, g.p.[+]	LC_{50}[*]
1,122	5 min	Rat	Lethal to some
842	30 min	Rat	LC_{50}
561	20 min	Rat	Loss of reflex, anesthesia
561	6 min	Mouse (anesthetized)	A-V block
561	5 min	Rat (anesthetized)	Cardiac arrythmias in all
140; 280; 561	5 min	Rat (unanesthetized)	Tachycardia, atrial fibrill., ventric. extrasystoles in some (incid. related to dose)
140-561	N.S.	Rat (anesthetized)	Bradycardia; also ectopic beats at 561 mg/m^3
337	4 hrs	Rat	Lethal to some
280	20 min or repeated daily	Rat, rabbit, dog	Biochemical changes indicative of slowed cellular respiration.
280	5 min	Monkey (anesthetized)	Tachycardia, ventric. premature beats, A-V block
280	5 min	Mouse, dog	SEIA[**]
140	5 min	Cardiomyopathic hamster	Cardiac arrythmias (compared to 561 x 10^3 mg/m^3 in normal hamsters)
140	5 min	Monkey (anesthetized)	Tachycardia
140	5 min	Monkey	SEIA
140	3.4 hr/day 20 days	Cat, g.p., rat	No signs of overt tox., no mortality
112	4 hrs	Cardiomyopathic hamster	High mortality and reduced lethal times compared to normal hamsters
70	3.5 hr/day 20 days	Dog	No signs of overt tox., no mortality
67	4 hr/day x 10 days	Rat	Respiratory and neuromusc. signs of tox., (recovery after expos). Pathology in brain liver, lungs; spleen changes
28-67	5 min	Dog	SEIA
58	8 hr/day x 30 days	Rat, g.p.	No significant signs of tox.
28	Brief	Monkey and dog	Influence on circulatory system
22	6 hr/day x 28 days	Rat, mouse, g.p., rabbit	No significant signs of tox.
5.6	90 days	Rat, g.p.	Lung, liver changes

[+] g.p. denotes guinea pig

[*] LC_{50} denotes median lethal concentration

[**] SEIA denotes sensitization to epinephrine-induced arrhythmia

TABLE 14

Inhalation Toxicology of F-12 (U.S. EPA, 1976)

Concentration of Vapor ($mg \times 10^3/m^3$)	Exposure, Duration or Regimen	Subject	Effect(s)
3,952	30 min	G.p.[+], rabbit, rat	LC_{50}[*]
3,754	30 min	Mouse	LC_{50}
2,470	1 hr	Rat	Anesthesia
2,638 (F11/F12, 1:1)	30	G.p.	LC_{50}
1,976	N.S.	Rat (anesthetized)	Arrhythmia in ¼; no ch. in heart rate
1,482-1,976	Brief (N.S.)	Rat	Tremors
1,482	30 min	Rat	LC_{50}
1,582 (F11/F12, 1:1)	30 min	Rat	LC_{50}
1,160 (F11/F12, 1:1)	30 min	Mouse	LC_{50}
988	5 min	Rat	Lethal to some
988	7-8 hr/day x 35-53 days	Dog, monkey	Tremors disappear after 2 wks-tolerance and depressed wt. gain
988	6 min	Mice (anesthetized)	No arrhythmias
494; 988; 1,976	N.S.	Rat (unanesthetized)	Tachycardia, no arrhythmias
494; 988	N.S.	Rat (anesthetized)	No change in heart rate, or arrhythmias
494	N.S.	Rat (anesthetized)	Arrhythmias in 10%
494	5 min	Monkey (anesthetized)	Arrhythmias
494	3.5 hr/day x 20 days	Rat, g.p., cat, dog	No mortal. and no overt signs of tox.
247	5 min	Monkey (anesthetized)	No arrhythmias
247	5 min	Dog	SEIA[**]
41	8 hr/day x 5 day/wk x 30 days	G.p.	Liver changes
4	Continuous, 90 days	G.p.	Liver changes

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[*] LC_{50} denotes median lethal concentration

[+] G.p. denotes guinea pig

[**] SEIA denotes sensitization to epinephrine-induced arrhythmia

TABLE 15

Bronchopulmonary and Cardiovascular Effects (other than arrhythmia) of F-11 and F-12 (U.S. EPA, 1976, data from Aviado, 1975b,c)

Effect	Subject	F-11		F-12	
		Conc.*	Intens.+	Conc.*	Intens.+
Tachycardia	Dog	56	+++	494	+
	Monkey	140	++	494	+
Myocardial depression	Dog	140	++		
	Monkey	140	++	494	+
Hypotension	Dog	140	++	0	
	Monkey	140	++	494	+
Early respiratory depression	Dog	561	+	988	+
	Monkey	280	+	0	+
	Mouse	140	++	247	+
	Rat	140	++	494	+
Bronchoconstriction	Dog	0		494	+
	Monkey	0		494	+
	Mouse	56	++	99	+
	Rat	140	++	0	
Decreased compliance	Dog	0		988	+
	Monkey	0		494	+
	Mouse	56	++	99	+
	Rat	140	++	494	+

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*Approx. minimal concentration ($10^3 mg/m^3$) producing response; 0 indicates absent or opposite responses

+1, 2 or 3 pluses indicate intensity of response

TABLE 16

Classification of Fluorocarbon and Other Propellant Compounds on the Basis of Cardiovascular and Bronchopulmonary Toxicity (U.S. EPA, data from Aviado, 1975b)

	Class and Compounds	Characteristics
I.	Low Pressure Propellants of High Toxicity CCl_3F (F-11), $CHCl_2F$(F-21) CCl_2F-$CClF_2$(F-113), CH_2Cl_2, and trichloroethane.	Toxic at 0.5-5% (v/v) in monkey and dog, and 1-10% in rat and mouse. Induce cardiac arrhythmias; sensitize heart to epinephrine-induced arrhythmias; cause tachycardia, myocardial depression, hypotension. Primarily cardiovascular effects.
II.	Low Pressure Propellants of Intermediate Toxicity $CClF_2$-$CClF_2$(F-114), $CClF_2$-CH_3(F-142b), isobutane and octafluorocyclobutane	Sensitize to epinephrine-arrhythmia in the dog at 5-25% (Cf. 0.5% or less for Class I). Do not induce arrhythmias in mouse (Class I do at 10-40%). Affect circulation in anesthetized dog and monkey at 10-20% (Cf at 0.5-2.5% for Class I). Cause bronchoconstriction in dog (Class I compounds do not), and, except in this respect, are less toxic than those in Class I. Cardiovascular effects predominate.
III.	High Pressure Propellants of Intermediate Toxicity CCl_2F_2(F-12),$CHClF_2$(F-22), propane, and vinyl chloride	Effective concentrations similar to Class II for cardiosensitization and circulatory effects, but respiratory depression and broncho-effects predominate over cardiovascular effects (in contrast to Classes I and II).
IV.	High Pressure Propellants of Low Toxicity F-115 and F-152b	Extent of circulatory effects less than those of Class III. Do not cause bronchoconstriction or early respiratory depression.

TABLE 17

Comparative Acute Toxicity Classification of Refrigerants (Underwriters Labs., 1971)

Toxicity class	Concentration, percent (v/v)	Exposure duration to produce death or serious injury in animals (hours)
1	0.5 - 1	0.83 (5min.)
2	0.5 - 1	0.5
3	2 - 2.5	1
4	2 - 2.5	2
5	Intermed.	Intermed.
6	20	No injury after 2 hrs

Several animal studies provide evidence that pre-existing cardiac or pulmonary lesions (diseased state) may enhance the toxicity (enhance toxic effect or reduce the level of exposure required to produce effect) of fluorocarbons (Taylor and Drew, 1975; Doherty and Aviado, 1975; Watanabe and Aviado, 1975). Also, Wills (1972) demonstrated a dose related (in range of 0.005 to 0.015 mg/kg) response to epinephrine (arrhythmic heart beats) in subjects briefly exposed to F-11 at 49×10^3 mg/m^3 (0.87 percent by volume). Thus, exposure to the fluorocarbons (such as from use of propellant bronchodilators or misuse of other products), in combination with use of cardioactive drugs or a stressful situation increasing endogenous epinephrine levels, could be hazardous and present a toxic risk greater than that from either factor alone (U.S. EPA, 1976; Howard, et al. 1974).

Pathologic liver changes were reported in guinea pigs chronically exposed (continuously for 90 days or eight hours daily, five days weekly, for six weeks) to F-12 at levels of about 4,000 mg/m^3 (0.08 percent by volume) (Prendergast, et al. 1967). In other chronic exposure experiments with rats, guinea pigs, monkeys, and dogs exposed to F-11 at 5,610 mg/m^3 for 90 days or at 57.5 x 10^3 mg/m^3 for eight hrs/day x five days/week x six weeks, pneumonitic changes were noted in all test groups (except in dogs exposed intermittently), liver changes were noted in rats and guinea pigs, and serum urea nitrogen was elevated in exposed dogs (Jenkins, et al. 1970). Several adverse changes were reported by Karpov (1963) in various species exposed to F-22 (in same class as and chemically similar to F-12) six hours daily for ten months at 50.1 x 10^3 mg/m^3 (1.42 percent, v/v), including: reduced endurance in swimming test and increased trials to establish conditioned reflex (mice); decreased oxygen consumption and increase in the stimulus strength required to induce response (rats); several hematologic and blood chemistry changes (rabbits) and degenerative pathoanatomic changes in heart, liver, kidney, nervous system, and lungs (Clayton, 1966).

Applications of F-11, F-12 and some mixed fluorocarbons repeated twice daily over several weeks to skin and oral mucosa of rats have produced irritation, edema, and inflammation. These effects were most marked in the F-11/F-22 mixture and in older subjects. The healing rate of burn lesions was retarded by appliations of F-11, F-12 and F-

22 (Quevauviller, et al. 1964; Quevauviller, 1965). The rapid evaporation of fluorocarbons applied directly to integumentary surfaces may result in chilling or freezing and may be the principal hazard in acute dermal exposure to the more volatile compounds. Dermal absorption and resulting systemic toxicity are more important in the less volatile fluorocarbons.

Information on oral route toxicity is limited (Howard, et al. 1974). Acute intragastric doses of F-11 at 7,380 mg/kg were reported as not lethal or grossly hepatoxic in rats (Slater, 1965), but Clayton (1966) noted that F-11 doses of 1,000 mg/kg (in peanut oil) were lethal in rats.

In one chronic (90 day) feeding study of F-12 in rats at 35 and 350 mg/kg/day Waritz (1971) reported somewhat elevated urinary fluoride and plasma alkaline phosphatase levels. No changes in dogs at 10 and 100 mg/kg/day were observed. In a two-year study using rats intubated with F-12 in corn oil at 15 and 150 mg/kg/day there was some suppression of weight gain at the high dose level, but no effects with respect to clinical signs, liver function, hematology, or histopathology were noted. In dogs given eight and 80 mg/kg daily in treated dog food there were no signs of toxicity, but some retention of F-12 (up to 1 mg/kg) in fat and bone marrow was observed (Sherman, 1974).

Synergism and/or Antagonism

Probably the most obvious concern in regard to this aspect is the cardiac sensitization by fluorocarbons to arrhythmogenic effects of circulating or administered catecholamines (e.g., epinephrine) or asphyxia. Stress situations or certain drugs taken in conjunction with or as a component of fluorocarbon propellant products may present an opportunity for synergistic consequences (Howard, et al. 1974).

Teratogenicity

There are no available data on the teratogenicity of halomethanes.

Mutagenicity

Information on the mutagenicity of halomethanes is very limited. Recently, however, three groups of investigators have reported positive results with certain alkyl halides in the Ames *Salmonella typhimurium* test system (Andrews, et al. 1976; Jongen, et al. 1978; Simmon, et al. 1977). Because of the formal relationship between molecular events involved in mutagenesis and carcinogenesis (Miller, 1978; Weinstein, 1978), the demonstration of mutagenic activity for a substance is often taken as presumptive evidence for the existence of carcinogenic activity as well. Therefore, it is believed that an investigation of the mutagenicity of xenobiotics may be predictive of carcinogenic potential (but not necessarily potency), and may serve as an early warning of a possible threat to human health where positive results are obtained.

Simmon and coworkers (1977) reported that chloromethane, bromomethane, bromodichloromethane, bromoform, and dichloromethane were all mutagenic to *Salmonella typhimurium* strain TA100 when assayed in a dessicator whose atmosphere contained the test compound. Metabolic activation was not required for the expression of mutagenic effect, since the addition of microsomes was not necessary. In all cases, the number of revertants per plate was directly dose-related.

Interpretation of these data with regard to carcinogenic risk, however, is complicated by several factors. Data were generally reported for only one Salmonella tester strain, and the vapor-phase exposure is one which is not extensively employed for mutagenesis testing. The number of plates assayed at each dose was not indicated, and the criteria used for determination of a significant mutagenic response were not specified. If the most stringent evaluation criteria were applied (in which the ratio of: experimental - control/control must exceed 2.5), bromoform and bromodichloromethane would not be considered positive in this study.

Confirmation of mutagenicity for all the chemicals examined by Simmon, et al. (1977) has not been reported by other investigators, either in the Ames assay or with other test systems. However, Andrews and coworkers (1976) have demonstrated that chloromethane was mutagenic to Salmonella typhimurium strain TA1535 in the presence and absence of added liver homogenate preparations. Simmon, et al. (1977) indicated that although dichloromethane was mutagenic in the Ames assay, it did not increase mitotic recombination in S. cerevisiae D3. In addition, it was reported that dichloromethane was negative on testing for mutagenicity in Drosophila (Filippova, et al. 1967).

The positive results for dichloromethane in the Ames assay were recently confirmed by Jongen, et al. (1978). Using Salmonella strains TA98 and TA100, which detect frameshift mutations, dose-related increases in mutation rate were obtained using vapor phase exposures (5,700 - 57,000 ppm). The addition of a microsomal preparation was not necessary for the production of mutations, although a slight enhancement in mutation rate could be obtained with rat liver homogenate. An explanation for why certain halomethanes are mutagenic in the Ames assay without the addition of a metabolic activating system has not been proposed.

Mutagenicity data on the fluorocarbons are scant. Upon incubation of labeled F-11 (also CCl_4, $CHCl_3$ and halothane) with liver microsomes and NADPH the label was found to be bound irreversibly to endoplasmic protein and lipid but was not detected in ribosomal RNA. None of the compounds was mutagenic in Salmonella tester strains TA1535 or 1538 with added liver microsomes (Uehleke, et al. 1977). Sherman (1974) found no increase in mutation rates over controls in a rat feeding study of F-12. Stephens, et al. (1970) reported significant mutagenic activity of F-12 at 2.47 x 10^6 mg/m^3 (50 percent) in air in a Neurospora crassa (a mold) test system.

Further testing is obviously required to establish the mutagneic potential of any or all of the halomethanes. Many investigators agree that a compound should demonstrate positive results in at least two different short-term assay systems before it is accepted as a mutagen/carcinogen. Nevertheless, based on the presently available mutagenicity data, it seems prudent to regard chloromethane, bromomethane, bromoform, dichloromethane, and bromodichloromethane as suspected mutagens/carcinogens pending the results of further research.

Carcinogenicity

Among the halomethanes, only chloroform, carbon tetrachloride, and iodomethane are generally regarded to be carcinogenic in animals (Natl. Acad. Sci., 1978). Limited new data, however, implicate several additional compounds as potential tumorigens. These data were developed using the strain A mouse lung tumor assay system, a bioassay which is known for its extremely high sensitivity to both strong and weak carcinogens (Shimkin and Stoner, 1975). The interpretation of lung tumor data in the strain A mouse is somewhat unique in that certain specific criteria should be met before a compound is considered positive:

(a) A significant increase in the mean number of lung tumors in test animals, preferably to one or more per mouse, should be obtained.

(b) A dose-response relationship should be evident.

(c) The mean number of lung tumors in control mice should be consistent with the anticipated incidence of spontaneous tumors for untreated strain A mice.

Theiss and coworkers (1977) examined the biological activity of bromoform, bromodichloromethane, and dichloromethane in strain A mice. Male animals, six to eight weeks old, were injected intraperitoneally up to three times weekly over a period of eight weeks. Three dose levels were employed with each test chemical, representing the maximum tolerated dose and a 1:2 and 1:5 dilution of the maximum tolerated dose. Twenty animals were used at each dose level, including negative (tricaprylin, saline) and positive (urethan) controls. Mice were sacrificed 24 weeks after the first injection and the frequency of lung tumors in each test group was statistically compared with that in the vehicle-treated controls using the Student t test.

The results obtained by Theiss, et al. (1977) are summarized in Table 18. These data indicate that in no case were all three criteria met, as indicated above, for the establishment of a positive response. Nevertheless, it is clear that bromoform produced a significant increase in tumor response at the intermediate dose. In addition, dichloromethane at the low dose only, and bromodichloromethane at the high dose only, produced results which were marginally significant. Overall, the results of this study are suggestive of carcinogenic activity but do not in themselves provide an adequate basis for the development of a quantitative health risk assessment for humans. Moreover, it has been stated with regard to the strain A mouse lung tumor system that, "positive compounds require extension to other systems, such as lifetime exposure of rats" (Shimkin and Stoner, 1975).

Unfortunately, there are little additional data to either confirm or deny the potential carcinogenicity of most halomethanes. Poirier and coworkers (1975) used the strain A mouse lung tumor system to show that iodomethane was tumorigenic. They concluded that, "a high proportion

TABLE 18

Pulmonary Tumor Response to Organic Water Contaminants
(Theiss, et al. 1977)

Compound	Vehicle	Dose/ injection (mg/kg)	No. of i.p. injections	Total dose (mg/kg)	No. of animals survivors/initial	No. of lung tumors/mouse	p
Tricaprylin	T[a]		24		15/20	0.27 ± 0.15[b]	
Bromoform	T	4	18	72	17/20	0.53 ± 0.21	0.335
		48	23	1,100	15/20	1.13 ± 0.36	0.041[c]
		100	24	2,400	15/20	0.67 ± 0.21	0.136
Bromodichloromethane	T	20	18	360	15/20	0.20 ± 0.11	0.724
		40	24	960	16/20	0.25 ± 0.11	0.930
		100	24	2,400	13/20	0.85 ± 0.27	0.067
Dichloromethane	T	160	17	2,720	18/20	0.94 ± 0.03	0.053
		400	17	6,800	5/20	0.80 ± 0.58	0.417
		800	16	12,800	12/20	0.50 ± 0.15	0.295
Urethan	S	1,000	1	1,000	20/20	19.6 ± 2.4	
0.9% NaCl solution	S		24		47/50	0.19 ± 0.06	

[a] Tricaprylin, S, 0.9% NaCl solution

[b] Average ± S.E.

[c] p 0.05

of low molecular weight alkyl halides may be carcinogenic." Thus, pending bioassay results on chloromethane and bromomethane, it may be prudent to regard these two compounds as suspected carcinogens, especially in light of their mutagenic effects in the Ames assay.

The potential carcinogenicity of dichloromethane is reportedly under study at the U.S. National Cancer Institute (NCI) using rats and mice treated by gavage (Natl. Cancer Inst., 1977). Dichloromethane has also been chosen by NCI for further testing by inhalation in mice and rats, and a study of bioactivation and covalent binding to macromolecules in mice, rats, and hamsters is planned (Natl. Cancer Inst., 1977, 1978).

Since the early 1960's a vast amount of work has been conducted on the ability of various chemicals to induce malignant transformation in cultured mammalian cells. Several of these _in vitro_ techniques have been adopted as convenient screening methods for the detection of potential carcinogens. Among the halomethanes, however, only dichloromethane has been investigated for cell transformation activity.

Price, et al. (1978) reported that Fischer rat embryo cells (F1706) were transformed by dichloromethane at high concentrations (1.6×10^{-3}M and 1.6×10^{-4}M) in the growth medium. In addition, transformed cells produced fibrosarcomas when injected subcutaneously into newborn rats.

Further research by Sivak (1978) has indicated, however, that the observed cell transforming capability of dichloromethane may have been due to impurities in the test material.

Sivak (1978) reported that when the experiments of Price, et al. (1978) were repeated using highly purified food grade dichloromethane no transformation occurred. Additional studies were conducted by Sivak (1978) in which food grade dichloromethane was tested in the BALD/C-3T3 mouse cell transformation assay system at three concentrations in the growth medium. Although transformed foci were observed at all dose levels, a dose-response relationship was not revealed, nor were the number of foci increased relative to historical results with untreated controls. Difficulty in the interpretation of these results, however, arises from the fact that dichloromethane (boiling point, 40°C) was added to the growth medium, and incubated at 37°C for 72 hours. Thus, the possibility exists that significant losses of the test material due to volatilization from the growth medium may have occurred.

The degree to which carcinogenic impurities may have accounted for the biological activity attributed to dichloromethane in *in vitro* test systems is not known. This problem may be particularly relevant to the halomethanes, since high concentrations of test chemical must be employed for expression of mutagenic/carcinogenic effects. It has been established that misleading results can be obtained with the Ames assay due to trace level contamination by carcinogenic impurities (Donahue, et al. 1978), and a similar situation probably exists with mammalian cell transformation assays. Sivak (1978) reported that impurities present in food grade dichloromethane included: cyclohexane (305 ppm), transdichloroethylene (86 ppm), vinyldene chloride (33 ppm), methyl bromide (11 ppm), chloroform ($<$10 ppm), carbon tetrachloride ($<$5 ppm) and ethyl chloride (3 ppm). Therefore, the results of sensitive assays in which technical grade material is employed must be interpreted with the knowledge that low level contamination may contribute to observed biological effects.

Carcinogenicity data on the fluorocarbons are scant. No human or animal data on carcinogenicity from exposure to F-11 or F-12 were available. However, concern about possible increased risk of cancer resulting indirectly from the use of fluorocarbons has developed in recent years. The possibility that increasing use and release of fluorocarbons to the atmosphere may contaminate the stratosphere and cause depletion of protective, ultraviolet-absorptive ozone has been recognized. The following adverse effects from increased penetration of UV radiation to the biosphere are suspected: (a) Increased incidence of skin cancer in humans (estimated at 20 to 35 percent increase for 10 percent ozone depletion); (b) altered animal cancer and disease patterns; (c) reduced growth and productivity of plants; (d) climatic changes and ecologic shifts (U.S. EPA, 1976).

A number of studies have sought to establish an association between trihalomethane levels in municipal drinking water supplies and the incidence of cancers in the U.S. population (Natl. Acad. Sci., 1978). Several of these epidemiologic studies have shown positive correlations between certain cancer death rates (various sites) and water quality indices, including water source, chlorination, and trihalomethanes (Cantor and McCabe, 1977, citing Cantor, et al. 1978 and Salg, 1977). Cantor, et al. (1978) have also reported positive associations between cancer mortality rates (several sites) and brominated trihalomethanes (BTHM). BTHM is comprised mostly of bromodichloromethane and chlorodibromomethane, but measurable levels of tribromomethane have been found in some water supplies. The authors caution that these studies have not been controlled for all confounding variables, and the limited monitoring data that were available may not have accurately reflected past exposures. Thus the need was recognized for further studies which will utilize exposure and disease information from individuals, rather than from population aggregates. However, based upon the epidemiologic evidence which is presently available, it is felt that sufficient justification exists for maintaining a hypothesis that observed positive correlations between drinking water quality and cancer mortality may be attributable to the presence of trihalomethanes (U.S. EPA, 1978a).

CRITERION FORMULATION

Existing Guidelines and Standards

Chloromethane

1. Warning label required by Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Interpretation with respect to warning, caution, and antidote statements required to appear on labels of economic poisons. 27 FR 2267.

2. Food tolerance requirement of Federal Food, Drug and Cosmetic Act: chloromethane is permitted as propellant in pesticide fomulations up to 30 percent of finished formulation when used in food storage/processing areas not contacting fatty foods. 27 FR 4623.

3. Human exposure: (1) A maximum permissible concentration (MPC) of 5 mg/m^3 in industrial plant atmospheres was established in Russia based on rat studies of chronic poisoning (Evtushenko, 1966); (2) OSHA (1976) has established the maximum acceptable time-weighted average air concentration for daily eight-hour occupational exposure at 210 mg/m^3 with ceiling and peak (five minutes during (or in) any three hours) concentration values of 413 and 620 mg/m^3, respectively.

4. Other: (1) Chlorinated hydrocarbons are under consideration for addition to the list of compounds for Toxic Effluent Standards (U.S. EPA Water Program Proposed Toxic Pollutant Effluent Standards. 40 CFR Part 129.(2) Listed on EPA Consent Decree Priority II list.

5. Multimedia Environmental Goals, (MEG) Estimated Permissible Concentrations (EPC) (U.S. EPA, 1977):

EPC, air, health: 0.5 mg/m^3
EPC, water, health (1): 7.5 mg/l
EPC, water, health (2): 2.9 mg/l
EPC, land, health: 5.8 mg/kg

Bromomethane

1. A warning and antidote labeling required by FIFRA. Interpretation with respect to warning, caution, and antidote statements required to appear on labels of economic poisons. 27 FR 2267.

2. Food tolerance limits required under Federal Food, Drug and Cosmetic Act Tolerances for residues of inorganic bromides resulting from fumigation with methyl bromide. 22 FR 5682 and subsequent regulations set inorganic bromide residue concentration limits for many food commodities at levels ranging from 20 to 400 mg/kg.

3. Human Exposure: (1) Occupational exposure during eight-hour work day limited to 78 mg/m^3 by the Texas State Department of Health; also regulated are use periods for respirators (Tex. State Dep. Health, 1957); (2) OSHA (1976) has established the eight-hour air concentration ceiling for occupational exposure at 80 mg/m^3, with an added warning of skin exposure hazard; (3) The (American National Standards Institute) has set a standard of 58 mg/m^3 time-weighted average air concentration for an eight-hour day, with interlocking period ceilings of 97 mg/m^3, and 194 mg/m^3 (five minutes) (Am. Natl. Stand. Inst., 1970); (4) The industrial

TLV (threshold limit value) of 78 mg/m^3 to prevent neurotoxic and pulmonary effects was established by the American Conference of Governmental Industrial Hygienist (Stokinger, et al. 1963; Am. Conf. Gov. Ind. Hy., 1971).

Dichloromethane

1. As an oil and fat solvent, dichloromethane is allowed in spice oleoresins at up to 30 mg/kg and in decaffeinated coffee at up to 10 mg/kg (21 CFR 121.1039, cited by Natl. Inst. Occup. Safety Health, 1976a).

2. Human exposure: (1) OSHA (1976) has established occupational exposure standards as follows: eight-hour time weighted average (TWA), 1,737 mg/m^3; acceptable ceiling concentration, 3,474 mg/m^3; and acceptable maximum peak above ceiling, 6,948 mg/m^3 (five minutes in any three hours). (2) However, in recognition of metabolic formation of COHb and additive toxicity with CO, NIOSH (1976a) has recommended a ten-hour workday TWA exposure limit of 75 ppm (261 mg/m^3) in the presence of no more CO than 9.9 mg/m^3 TWA and a 1,737 mg/m^3 peak (15 min. sampling); in the case of higher CO levels, lower levels of dichloromethane are required; (3) Permissible exposure levels in several other countries range from 49 up to 1,737 mg/m^3 (maximum allowable concentration) or 2,456 mg/m^3 (peak) (discussed in Natl. Inst. Occup. Safety Health, 1976a); (4) The maximum permissable concentration for dichloromethane in water in the U.S.S.R. is 7.5 mg/l; this is intended to be proportionately reduced in the presence of other limited compounds (Stofen, 1973).

3. MEG values for Estimated Permissible Concentrations (U.S. EPA, 1977):

EPC, air, health:	0.619 mg/m^3
EPC, water, health (1)	9.18 mg/l
EPC, water, health (2)	3.59 mg/l
EPC, land, health:	7.2 mg/kg

Tribromomethane

Human exposure: (1) The OSHA Occupational Exposure Standard for workroom air (eight-hour TWA) is 5 mg/m^3, with a dermal absorption warning notation (Occup. Safety Health Admin., 1976); (2) Tribromomethane is one of four trihalomethanes comprising the group "total trihalomethanes" (TTHM) for which the U.S. EPA has proposed to regulate a maximum contaminant level in drinking water (0.100 mg/l).

Bromodichloromethane

Human exposure: (1) There is no currently established occupational exposure standard for bromodichloromethane in the U.S. (2) Bromodichloromethane, along with chlorodibromomethane, trichloromethane (chloroform) and tribromomethane form the group of halomethanes termed total trihalomethanes (TTHM), which are to be regulated in finished drinking water in the U.S. The maximum permissible concentration set for TTHM in the proposed regulations is 0.100 mg/l.

Trichlorofluoromethane and Dichlorodifluoromethane

Food use: FDA regulations permit use of dichlorodifluoromethane (F-12) as a direct contact freezing agent for food, and specify labeling and instructions for use. Food and Drug Administration. Dichlorodifluoromethane. 32 FR 6739.

Human exposure: (1) The current OSHA eight-hour TWA occupational standards for F-11 and F-12 are 5,600 and 4,950 mg/m^3, respectively (Occup. Safety Health Admin., 1976). (2) Underwriters Laboratories classify F-11 and F-12 in groups 5 and 6, respectively (see Effects section).

Other: (1) F-11, F-12, and several other fluorocarbons have been exempted from regulation under the Texas Clean Air Act (Howard, et al. 1974); (2) The U.S. EPA can control fluorocarbon uses in pesticide applications and has requested formulators to seek suitable alternative propellants for products dispensed as aerosols, in view of the ozone depletion concern; (3) Pressurized containers must meet ICC regulations for compressed gases to be shipped (Howard, et al. 1974, citing DuPont, 1973).

Standard for regulation of trihalomethanes: The U.S. EPA has considered the available health and exposure data for trihalomethanes as a group, determined that they represent a potential yet reducible hazard to public health, and proposed regulations establishing a maximum contaminant level (MCL) of 0.100 mg/l for total trihalomethanes (TTHM) in finished drinking water of cities greater than 75,000 (served population) employing added disinfectants (U.S. EPA, 1978a).A detailed discussion of the background (rationale, extrapolation models, and interpretations used) for this standard is beyond the scope of this document.

Special Groups at Risk

Perhaps the greatest concern for special risk considerations among the halomethanes is that for dichloromethane.

In this case, the added threat is for those such as smokers or workers in whom significant COHb levels exist, or those with pre-existing heart disease, for whom COHb formation by dichloromethane metabolism would present an added stress or precipitate an episode from disturbed oxygen transport. NIOSH, recognizing this combined stress hazard, has recommended lowering the existing TLV for dichloromethane and tying it with existing CO exposure levels.

A second possible special risk concerns exposures to fluorocarbon vapors. In this case there is evidence that a characteristic toxicity involves sensitization to cardio-arrhythmogenic effects of endogenous or administered epinephrine and related catecholamines. An individual with cardiac disease taking certain medication or in an acutely stressed state may be especially susceptible to fluorocarbon cardiotoxicity.

Basis and Derivation of Criterion

Data on current levels of the halomethanes in water, food, and ambient air are not sufficient to permit adequate estimates of total human exposures from these media. Available data discussed in an earlier section of this report (Occurrence) indicate that the greatest human exposure to the trihalomethanes occurs through the consumption of liquids (including drinking water and beverages containing it), and that exposure to chlorofluorocarbons, chloromethane, dichloromethane,and bromomethane occurs primarily by inhalation.

Observed correlations among concentrations of trihalomethanes in finished water are attributed to the presence of common organic precursor materials in raw water (Natl. Acad. Sci., 1978). Among the halomethanes considered in this report, bromodichloromethane seems to predominate in drinking waters. Concentrations of bromodichloromethane in raw and finished water samples are generally in the area of 6 µg/l or less, and thus represent a reasonable upper limit for anticipated levels of any halomethane in water (excluding chloroform and carbon tetrachloride).

Recent reports showing that chloromethane, bromomethane, tribromomethane, dichloromethane, and bromodichloromethane exhibit carcinogenic and/or mutagenic effects in certain bioassay systems suggests the need for conservatism in the development of water quality criteria for the protection of human health. Since the presently available carcinogenicity data base for these compounds is judged qualitatively informative but quantitatively inadequate for risk extrapolation, an alternative approach is necessary for criteria development.

At present levels in relatively unpolluted raw and finished waters (10 µg/l), the halomethanes pose little threat for the production of non-carcinogenic toxic effects in humans. However, the possibility of carcinogenic effects must be evaluated in light of current and past exposures to halomethanes via water supplies. Limited epidemiologic studies have failed to show a clear association between cancer mortality and bromine-containing trihalomethanes at levels in water of about 5-10 µg/l. Since the possible association between human cancers and halomethanes cannot presently be disproven, it would be wise to limit their presence in water to no more than the median levels which are currently encountered (pending better human risk data). Thus, a maximum level of 6 ug/l in raw and finished waters could be considered as acceptable for bromethane, chloromethane, dichloromethane, tribromomethane, and bromodichloromethane. From the limited animal bioassay data which are available in the strain A mouse lung tumor system, a daily human intake of halomethanes at 12 ug/day (6 ug/l x 2 l/day) represents a dose which is about 100,000-fold less than the minimum daily dose of tribromomethane which caused a significant increase in tumor formation in mice if dose comparisons for the two species are made on a per kilogram body weight basis. Since there exists considerable uncertainty over the human carcinogenic risks of halomethanes, a safety factor of 100,000 seems prudent for the development of an interim standard for all halomethanes pending the results of further research.

The 6 ug/l maximum acceptable concentration for bromomethane, chloromethane, tribromomethane, dichloromethane, and bromodichloromethane does not take into consideration the contribution to total exposure from air and food. Exposure via these media cannot be accurately predicted, although it is likely that it is sufficient large for chloromethane, dichloromethane, and bromomethane to warrant the recommendation of a water quality criterion below 6 ug/l. Present levels of these three compounds are generally much less than 6 ug/l and it is not likely that current anthropogenic sources would significantly increase their level in water.

For criteria-setting purposes it is recommended that a criterion of 2 ug/l be adopted for branomethane, chloromethane, dichloromethane, tribromomethane, and bromodichloromethane, based upon analogy to the structure and biological activity of chloroform. Despite the presently inadequate data base for most of these compounds, it can nevertheless be predicted that similar biological effects, including neoplastic transformation, may be encountered. Since the recommended criterion for chloroform was derived from reliable experimental data, it represents the most applicable value for all of the halomethanes which are suspected carcinogens.

Evidence for mutagenicity of dichlorodifluoromethane is equivocal and there is no evidence as yet for carcinogenicity as a result of direct exposure. Chronic toxicity data for dichlorodifluoromethane is quite limited. In the only long-term (two years) feeding study reported (U.S. EPA, 1976, citing Sherman, 1974) the maximum dose level producing no observed adverse effect (in dogs) was 80 mg/kg/day. Applying an uncertainty factor of 1000 (Natl. Acad. Sci., 1977) to this data yields a presumptive "acceptable daily intake" of 0.08 mg/kg/day. For a man weighing 70 kg, consuming two liters of water per day and absorbing at 100 percent efficiency, and assuming that the water is the sole source of exposure, this acceptable intake level translates into a criterion level as follows: (0.08) (70)/2 = 2.8 mg/l.

There is no evidence for mutagenicity of trichlorofluoromethane, and no evidence as yet for carcinogenicity as a result of direct exposure. The only data on toxicity testing using prolonged exposure at relatively low test concentrations is from a report (Jenkins, et al. 1970) which showed no observed adverse effects in rats and guinea pigs exposed continuously by inhalation for 90 days at 5,610 mg/m^3. If the reference man weighing 70 kg breathed this atmosphere and absorbed the compound at 50 percent efficiency, his estimated exposure dose would be 5,610 x 23 x 0.5 = 64,515 mg/day or 922 mg/kg/day. Applying an uncertainty factor of 1,000 (Natl. Acad. Sci., 1977) to this data yields a presumptive "acceptable daily intake" of 0.922 mg/kg/day for trichlorofluoromethane. Assuming man's weight to be 70 kg and his absorption of ingested compound to be 100 percent efficient, and that his sole source of exposure is water consumed at two liters/day, the acceptable intake is translated into a criterion level as follows: (0.922) (70)/2 = 32.3 mg/l.

Criterion levels intended to protect the public against unacceptable risk of toxicity, mutagenicity, or carcinogenicity from exposure to selected halomethanes in water for consumption, derived as described in the foregoing text, are summarized as follows (rounded off):

Compound	(mg/l)
Bromodichloromethane	2×10^{-3}
Tribromomethane	2×10^{-3}
Dichloromethane	2×10^{-3}
Bromomethane	2×10^{-3}
Chloromethane	2×10^{-3}
Dichlorodifluoromethane	3
Trichlorofluoromethane	32

Adoption of the presently recommended criterion for chloroform (2 µg/l) as the recommended level for other possibly carcinogenic halomethanes should provide an adequate margin of safety in the absence of sufficient data for quantitative risk assessment. This criterion is intended to reduce carcinogenic risks to the public, and takes into account the fact that exposure to halomethanes also occurs through foods and via inhalation. Although the potential carcinogenicity of bromodichloromethane, tribromomethane, dichloromethane, bromomethane, and chloromethane cannot be adequately assessed at present, the adoption of an interim water quality standard in excess of 2 µg/l may be interpreted as approval to discharge larger quantities of these substances than of chloroform. Such a practice is clearly unwarranted until such time that concerns over possible carcinogenic activity have been resolved.

APPENDIX I

Summary and Conclusions Regarding the Carcinogenicity of Halomethanes*

The halomethanes addressed in this report are bromomethane, chloromethane, dichloromethane, tribromomethane, bromodichloromethane, dichlorodifluoromethane, and trichlorofluoromethane. Chloroform, which is also a trihalomethane, is discussed in another document.

Positive associations between cancer mortality rates in humans and trihalomethanes in drinking water have been reported. In addition to chloroform, these trihalomethanes consisted primarily of bromodichloromethane, chlorodibromomethane, and also barely measurable levels of tribromomethane. There have been positive results for tribromomethane using strain A/St. male mice in the pulmonary adenoma bioassay. Bromomethane, chloromethane, dichloromethane, bromodichloromethane, and tribromomethane have been reported as mutagenic in the Ames' test without metabolic activation. Dichlorodifluoromethane caused a significant increase in mutant frequency in Neurospora crassa (mold), but was negative in the Ames' test. No data implicating trichlorofluoromethane as a possible carcinogen have been published.

Because positive results for the mutagenic endpoint correlate with positive results in in vivo bioassay for oncogenicity, mutagenic data for the halomethanes suggests that several of the compounds might be carcinogenic. Carcinogenicity data currently available for the halomethanes are not adequate for the development of water criteria levels. We suggest that the criteria level be the same as that for chloroform (2 ug/l).

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*This summary has been prepared and approved by the Carcinogens Assessment Group, EPA, June, 1979.

REFERENCES

Ahmed, A.E., et al. 1977. Metabolism of haloforms to carbon monoxide, I. In vitro studies. Drug Metab. Dispos. 5: 198. (Abstract.)

Allen and Hanbury. 1971. An investigation of possible cardiotoxic effects of the aerosol propellants, Arctons 11 and 12. Vol. 1. Unpubl. Rep.

American Conference of Governmental and Industrial Hygienists. 1971. Documentation of the threshold limit values for substances in workroom air. Cincinnati, Ohio.

American National Standards Institute. 1970. American national standard for acceptable concentrations of methyl bromide (monobromomethane). ANSI Z37.24.

Andrews, A.W., et al. 1976. A comparison of the mutagenic properties of vinyl chloride and methyl chloride. Mutat. Res. 40: 273.

Araki, S., et al. 1971. Methyl bromide poisoning. A report based on fourteen cases. Jap. Jour. Ind. Health 13: 507.

Archer, V.E. 1973. Letter to editor. Br. Med. Jour. 3: 5882.

Astrand, I., et al. 1975. Exposure to methylene chloride. I. Its concentration in alveolar air and blood during rest and exercise and its metabolism. Scand. Jour. Workplace Environ. Health 1: 78.

Aviado, D.M. 1975a. Toxicity of aerosol propellants on the respiratory and circulatory systems. IX. Summary of the most toxic: Trichlorofluoromethane (FC-11). Toxicology 3: 311.

Aviado, D.M. 1975b. Toxicity of aerosol propellants on the respiratory and circulatory systems. X. Proposed classification. Toxicology 3: 321.

Aviado, D.M. 1975c. Toxicity of aerosols. Jour. Clin. Pharmacol. 15: 86.

Avilova, G.G., et al. 1973. Itogi Navki Tekh., Farmakol., Khimioter. Svedstva, Toksikol. Probl. Toksikol. (Russian) 5: 92. (Abstract.)

Azar, A., et al. 1972. Experimental human exposures to fluorocarbon 12 (dichlorofluoromethane). Am. Ind. Hyg. Assoc. Jour. 33: 207.

Azar, A., et al. 1973. Blood levels of fluorocarbon related to cardiac sensitization. Am. Ind. Hyg. Assoc. Jour. 34: 102.B

Baird, T.T. 1954. Methyl chloride poisoning. Br. Med. Jour. 2: 1353.

Balander, P.A., and M.G. Polyak. 1962. Toxicological characterization of methyl bromide. Gigiena i Toksikol. Novykh. Pestitsidov i Klinika Otravlenii, Dokl. 2-oi (Vtoroi) Vses. Konf. 412.

Ballantyne, B., et al. 1976. The ophthalmic toxicology of dichloromethane. Toxicology 6: 173.

Balmer, M.F., et al. 1976. Effects in the liver of methylene chloride inhaled alone and with ethyl alcohol. Am. Ind. Hyg. Assoc. Jour. 37: 345.

Barnsley, E.A. 1964. The metabolism of S-methyl-L-cysteine in the rat. Biochem. Biophys. Acta 90: 24.

Barnsley, E.A., and L. Young. 1965. Biochemical studies of toxic agents. The metabolism of iodomethane. Biochem. J. 95: 77.

Bass, M. 1970. Sudden sniffing death. Jour. Am. Med. Assoc. 212: 2075.

Benatt, A.J., and T.R.B. Courtney. 1948. Uraemia in methyl bromide poisoning: Case report. Br. Jour. Ind. Med. 5: 21.

Blake, D.A., and G.W. Mergner. 1974. Inhalation studies on the biotransformation and elimination of (^{14}C)-trichlorofluoromethane and (^{14}C)-dichlorodifluoromethane in beagles. Toxicol. Appl. Pharmacol. 30: 396.

Boyland, E., et al. 1961. Metabolism of polycyclic compounds. 18. The secretion of naphthalene 1:2-dihydronaphthlene and 1:2 epoxy-1,2,3,4-tetrahydronapthalene in rat bile. Biochem. Jour. 78:376.

Bowman, F.G., et al. 1978. The toxicity of some halomethanes in mice. Toxicol. Appl. Pharmacol. 44: 213.

Bridbord, K., et al. 1974. Exposure to halogenated hydrocarbons in the indoor environment. Presented at Conf. Publ. Health Implications of Plastic Manufacturing, Pinehurst, N.C.

Browning, E. 1965. Toxicity and metabolism of industrial solvents. Elsevier Publishing Co., Amsterdam.

Bruhin, J. 1943. Deutsches Gesund Gerichtles Medicine 37, A253. Thesis. Zurich, Switzerland. (See von Oettingen, 1964).

Campbell, K. 1978. Unpubl. data.

Cantor, K.P., and L.J. McCabe. 1977. The epidemiologic approach to the evaluation of organics in drinking water. Proc. Conf. Water Chlorination: Environ. Impact and Health Effects. Gatlinburg, Tenn. Oct. 31 - Nov. 4.

Cantor, K.P., et al. 1978. Associations of halomethanes in drinking water with cancer mortality. Jour. Natl. Cancer Inst. (In press.)

Carlsson, A., and M. Hultengren. 1975. Exposure to methylene chloride, III. Metabolism of ^{14}C-labeled methylene dichloride in rat. Scand. Jour. Work Environ. Health 1: 104.

Carter, V.L., et al. 1970a. Effects of inhalation of freon 113 on laboratory animals. Rep. AD 727524. U.S. Natl. Tech. Inf. Serv.

Carter, V.L., et al. 1970b. Effect of bromotrifluoromethane on operant behavior in monkeys. Toxicol. Appl. Pharmacol. 17: 307.

Chiou, W.L., and S. Niazi. 1973. A simple and ultra-sensitive headspace gas chromatographic method for the assay of fluorocarbon propellants in blood. Res. Commun. Chem. Pathol. Pharmacol. 6: 481.

Chopra, N.M., and L.R. Sherman. 1972. Systemic studies on the breakdown of p,p'-DDT in tobacco smokes. Anal. Chem. 44: 1036.

Clark, D.G., and D.J. Tinston. 1972a. The influence of fluorocarbon propellants on the arrythmogenic activities of adrenaline and isoprenaline. Proc. Eur. Soc. Study Drug Toxicity. 13: 212.

Clark, D.G., and D.J. Tinston. 1972b. Cardiac effects of isoproterenol, hypoxia, hypercapnia and fluorocarbon propellants and their use in asthma inhalers. Ann. Allergy. 30: 536.

Clarke, C.A., et al. 1945. Methyl bromide poisoning: Account of four recent cases met with in one of H.M. Ships. Br. Jour. Ind. Med. 2: 17.

Clayton, J.W. 1966. The mammalian toxicology of organic compounds containing fluorine. Handbuch Exp. Pharmakol. 20: 459.

Collier, H. 1936. Methylene dichloride intoxication industry-- a report of two cases. Lancet 1: 594.

Collins, R.P. 1965. Methyl bromide poisoning: A bizarre neurological disorder. Calif. Med. 103: 112.

Cordle, F., et al. 1978. Human exposure to polychlorinated biphenyls and polybrominated biphenyls. Environ. Health Perspect. 24: 157.

Cox, P.J., et al. 1972. A comparison of the interactions of trichlorofluoromethane and carbon tetrachloride with hepatic cytochrome P-450. Biochem. Jour. 130: 87.

Cox, R.A., et al. 1976. Photochemical oxidation of halocarbons in the troposphere. Atmos. Environ. 10: 305.

Cronn, D.R., et al. 1976. Measurement of tropospheric halocarbon by gas chromatography - mass spectrometry. Rep. Phase I of EPA Grant No. R0804033-01. U.S. Environ. Prot. Agency, Research Triangle Park, N.C.

Davis, L.N., et al. 1977. Investigation of selected potential environmental contaminants: monohalomethanes. EPA 560/2-77-007; TR 77-535. Final rep. June, 1977, on Contract No. 68-01-4315. Off. Toxic Subst. U.S. Environ. Prot. Agency, Washington, D.C.

Dennis, N.M., et al. 1972. Formation of methyl chloride during methyl bromide fumigations. Jour. Econ. Entomol. 65: 1753.

Department of Health, Education, and Welfare. 1975. Registry of toxic effects of chemical substances. Washington, D.C.

DiVincenzo, G.D., and M.L. Hamilton. 1975. Fate and disposition of (^{14}C) methylene chloride in the rat. Toxicol. Appl. Pharmacol. 32: 385.

DiVincenzo, G.D., et al. 1972. Human and canine exposures to methylene chloride vapor. Am. Ind. Hyg. Assoc. Jour. 33: 125.

Dixon, M., and D.M. Needham. 1946. Biochemical research on chemical warfare agents. Nature 158: 432.

Doherty, R.E., and D.M. Aviado. 1975. Toxicity of aerosol propellants on the respiratory and circulatory systems. VI. Influence of cardiac and pulmonary vascular lesions in the rat. Toxicology 3: 213.

Donahue, E.V., et al. 1978. Detection of mutagenic impurities in carcinogens and noncarcinogens by high-pressure liquid chromatography and the Salmonella/Microsome test. Cancer Res. 38: 431.

Drawneek, W., et al. 1964. Industrial methylbromide poisoning in fumagators. Lancet 2: 855.

Dunavskii, G.A. 1972. Functional condition of circulatory organs in workers employed in the production of organochlorine compounds. Gig. Tr. Prof. Zabol. (Russian) 16: 48. (Abstract.)

DuPont de Nemours and Co. 1968. Human skin absorption studies with trichlorotrifluoroethane, F-113. Med. Res. Proj. Rep. No. 84-68.

DuPont de Nemours and Co. 1973. Interstate Commerce Commission regulations and containers for freon fluorocarbons. Bull. D-75.

Dykan, V.A. 1962. Changes in liver and kidney functions due to methylene bromide and bromoform. Nauchn.-Trudy Ukr Nauchn.-Issled. Inst. Gigieny Truda i Profzabolevanii 29: 82.

Eddy, C.W., and F.D. Griffith. 1961. Metabolism of ^{14}C-dichlorodifluoromethane by rats. Presented at Am. Ind. Hyg. Assoc. Conf. Toronto, Can. May, 1971.

Evtushenko, G.Y. 1966. Methyl chloride toxicology. Gig. Tr. Prof. Zabol. 10: 20.

Fassett. 1978. In forum discussion, Session II, Toxicity of halogenated solvents, aerosol propellants, and fire-extinguishants. Proc. 3rd Annu. Conf. Environ. Toxicol. AMRL-TR-72-130. Aerospace Med. Res. Lab., Wright-Patterson Air Force Base, Ohio.

Filippova, L.M., et al. 1967. Chemical mutagens. IV. Mutagenic activity of geminal system. Genetika 8: 134.

Fodor, G.G., and A. Roscovanu. 1976. Increased blood-CO-content in humans and animals by incorporated halogenated hydrocarbons. Zentralbl Bakteriol (Orig B) (German) 162: 34. (Abstract.)

Getzendaner, M.E., et al. 1968. Bromide residues from methyl bromide fumigation of food commodities. Jour. Agric. Food Chem. 16: 265.

Good, W.O., et al. 1975. Sputum cytology among frequent users of pressurized spray cans. Cancer Res. 35: 316.

Gorbachev, E.M., et al. 1962. Disturbances in neuroendocrine regulation and oxidation-reduction by certain commercial poisons. Plenuma Patofiziol Sibiri i Dal'n. Vost. Sb. 88.

Greenberg, J.O. 1971. The neurological effects of methyl bromide poisoning. Ind. Med. and Surg. 40: 27.

Grimsrud, E.P., and R.A. Rasmussen. 1975. Survey and analysis of halocarbons in the atmosphere by gas chromatography-mass spectrometry. Atmos. Environ. 9: 1014.

Hansen, H., et al. 1953. Methyl chloride intoxication: Report of 15 cases. AMA Arch. Ind. Hyg. Occup. Med. 8: 328.

Harsch, D. 1977. Study of halocarbon concentrations in indoor environments. Final rep. EPA Contract No. WA 6-99-2922-J. U.S. Environ. Prot. Agency, Washington, D.C.

Harsch, D., and R.A. Rasmussen. 1977. Identification of methyl bromide in urban air. EPA Contract No. WA 6-99-2922-J. Off. Res. Dev., U.S. Environ. Prot. Agency, Washington, D.C. (unpubl. rep.)

Haun, C., et al. 1972. Continuous animal exposure to low levels of dichloromethane. Proc. 3rd Annu. Conf. Environ. Toxicol. AMRL-TR-130: 12. Aerospace Med. Res. Lab., Wright Patterson Air Force Base, Ohio.

Health and Welfare Canada. 1977. Environmental Health Directorate national survey of halomethane in drinking water.

Heppel, L.A., and P.A. Neal. 1944. Toxicology of dichloromethane (methylene chloride) II. Its effect upon running activity in the male rat. Jour. Ind. Hyg. Toxicol. 26: 17.

Hester, N.E., et al. 1974. Fluorocarbons in the Los Angeles basin. Air Pollut. Control Assoc. Jour. 24: 591.

Hine, C.H. 1969. Methyl bromide poisoning. Jour. Occup. Med. 11: 1.

Howard, P., and A. Hanchett. 1975. Chlorofluorocarbon sources of environ-contamination. Science 189: 217.

Howard, P.H., et al. 1974. Environmental hazard assessment of one and two carbon fluorocarbons. EPA 560/2-75-003. TR-74-572.1. Off. Toxic Subst. U.S. Environ. Prot. Agency, Washington, D.C.

Hughes, J.P. 1954. Hazardous exposure to some so-called safe solvents. Jour. Am. Med. Assoc. 156: 234.

International Agency for Research on Cancer. 1978. Information bulletin on the survey of chemicals being tested for carcinogenicity, No. 7. World Health Organ., Lyon, France

Irish, D.D., et al. 1940. The response attending exposure of laboratory animals to vapors of methyl bromide. Jour. Ind. Hyg. Toxicol. 22: 218.

Irish, D.D., et al. 1941. Chemical changes of methyl bromide in the animal body in relation to its physiological effects. Jour. Ind. Hyg. Toxicol. 23: 408.

Jenkins, L.J., et al. 1970. Repeated and continuous exposure of laboratory animals to trichlorofluoromethane. Toxicol. Appl. Pharmacol. 16: 133.

Johnson, M.K. 1966. Metabolism of iodomethane in the rat. Biochem. Jour. 98: 38.

Johnstone, R. 1945. Methyl bromide intoxication of large group of workers. Ind. Med. 14: 495.

Jongen, W.M.F., et al. 1978. Mutagenic effect of dichloromethane on Salmonella typhimurium. Mutat. Res. 56: 245.

Kakizaki, T. 1967. Studies on methyl bromide poisoning. Ind. Health 5: 135.

Karpov, B.C. 1963. Tr. Leningr. Sanit.-Gigien. Med. Inst. 75: 231. (Summarized in Clayton, 1966.)

Kehoe, R.A. 1943. Unpublished report. (Cited in Azar, et al. 1972.)

Killen, S.M., and W.S. Harris. 1972. Direct depression of myocardial contracility by the aerosol propellant gas, dichlorodifluoromethane. Jour. Pharm. Exp. Ther. 183: 245.

Kleopfer, R.D. 1976. Analysis of drinking water for organic compounds. Identification and analysis of organic pollutants in water. Ann Arbor Science, Ann Arbor, Mich.

Knight, H.D., and M. Reina-Guerra. 1977. Intoxication of cattle with sodium bromide-contaminated feed. Am. Jour. Vet. Res. 38: 407.

Krey, P.W., et al. 1976. Stratospheric concentrations of CCl_3F in 1974. Jour. Geophys. Res. 81: 1557.

Kubota, S. 1955. Industrial poisoning in chemical plants. I. Methyl bromide poisoning. Jour. Soc. Org. Synth. Chem. 13: 605.

Kutob, S.D., and G.L. Plaa. 1962. A procedure for estimating the hepatotoxic potential of certain industrial solvents. Toxicol. Appl. Pharmacol. 4: 354.

Lebowitz, M.D. 1976. Aerosol usage and respiratory symptoms. Arch. Environ. Health 31: 83.

Lehmann, K.B., and I. Schmidt-Kehl. 1936. The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene. Arch. Hyg. 116: 131.

Lewis, S.E. 1948. Inhibition of SH enzymes by methyl bromide. Nature 161: 692.

Lillian, D., and H.B. Singh. 1974. Absolute determination of atmospheric halocarbons by gas phase conlometry. Anal. Chem. 46: 1060.

Lillian, D., et al. 1975. Atmospheric fates of halogenated compounds. Environ. Sci. Technol. 9: 1042.

Longley, E.O., and A.T. Jones. 1965. Methyl bromide poisoning in man. Ind. Med. Surg. 34: 499.

Lovelock, J.E. 1971. Atmospheric fluorine compounds as indicators of air movements. Nature 230: 379.

Lovelock, J.E. 1972. Atmospheric turbidity and CCl_3F concentrations in rural southern England and southern Ireland. Atmos. Environ. 6: 917.

Lovelock, J.E. 1974. Atmospheric halocarbons and stratospheric ozone. Nature 252: 292.

Lovelock, J.E. 1975. Natural halocarbons in the air and in the sea. Nature 256: 193.

Lovelock, J.E., et al. 1973. Halogenated hydrocarbons in and over the Atlantic. Nature 241: 194.

Lynn, G.E., et al. 1963. Occurrence of bromide in the milk of cows fed sodium bromide and grain fumigated with methyl bromide. Jour. Agric. Food Chem. 11: 87.

MacDonald, J.D.C. 1964. Methyl chloride intoxication. Jour. Occup. Med. 6: 81.

Marier, G., et al. 1973. Blood fluorocarbon levels following exposures to a variety of household aerosols. Household Pers. Prod. Ind. 10: 68.

Matsumoto, T., et al. 1968. Aerosol tissue adhesive spray: Fate of freons and their acute topical and systemic toxicity. Arch. Surg. 97: 727.

McConnell, G., et al. 1975. Chlorinated hydrocarbons and the environment. Endeavour 34: 13.

Mellerio, F., et al. 1973. Electroencephalography and acute methyl bromide poisoning. Electroencephalogr. Clin. Neurophysiol. 34: 732.

Mellerio, F., et al. 1974. Electroencephalographie au cours des intoxicantions aiques par brocure de methyle. Jour. Eur. Toxicol. 7: 119.

Metcalf, R.L., and P.Y. Lu. 1973. Environmental distribution and metabolic fate of key industrial pollutants and pesticides in a model ecosystem. Univ. Illinois Water Resour. Center, UILU-WRC-0069. PB 225479, Natl. Tech. Inf. Serv., Springfield, Va.

Miller, D.P., and H.W. Haggard. 1943. Intracellular penetration of bromide as feature in toxicity of alkyl bromides. Jour. Ind. Hyg. Toxicol. 25: 423.

Miller, E.C. 1978. Some current perspectives on chemical carcinogenesis in humans and experimental animals: presidential address. Cancer Res. 38: 1479.

Miller, J.W. 1943. Fatal methyl bromide poisoning. Arch. Pathol. 36: 505.

Mizyokova, I.G., and G.N. Bakhishev. 1971. Specific treatment of acute methylbromide poisoning. Vrach. Delo. 7: 128.

Monro, H.A.U., et al. 1955. Methyl bromide concentrations in ship and railway car fumigation of peanuts. Entomol. Soc. Ontario, Annu. Rep. 86: 65.

Morgan, A., et al. 1967. Studies on the retention and metabolism of inhaled methyl iodine. II. Metabolism of methyl iodide. Health Physics 13: 1067.

Morgan, A., et al. 1972. Absorption and retention of inhaled fluorinated hydrocarbon vapors. Int. Jour. Appl. Radiat. Isotop. 23: 285.

Morgan, A.J. 1942. Methyl chloride intoxication. Q. Jour. Med. 41: 29.

Morris, J.C., and G. McKay. 1975. Formation of halogenated organics by chlorination of water supplies. EPA 600/1-75-002. PB 241-511. Natl. Tech. Inf. Serv., Springfield, Va.

Moskowitz, S., and H. Shapiro. 1952. Fatal exposure to methylene chloride vapor. Arch. Ind. Hyg. Occup. Med. 6: 116.

Munson, A.E., et al. 1977. Functional activity of the reticuloendothelial system in mice exposed to haloalkanes for ninety days. Abstract. 14th Natl. Reticuloendothelial Soc. Meet. Tucson, Ariz. Dec. 6-9.

Munson, A.E., et al. 1978. Reticuloendothelial system function in mice exposed to four haloalkanes: Drinking water contaminants. Submitted: Soc. Toxicol. (Abstract.)

National Academy of Sciences. 1977. Drinking water and health. Washington, D.C.

National Academy of Sciences. 1978. Nonfluorinated halomethanes in the environment. Washington, D.C.

National Cancer Institute. 1977. Chemicals being tested for carcinogenicity by the bioassay program. Rep. Tech. Inf. Resour. Branch, Natl. Cancer Inst., U.S. Dep. Health, Edu. and Welfare, Bethesda, Md.

National Cancer Institute. 1978. Personal communication.

National Institute for Occupational Safety and Health. 1976a. Criteria for a recommended standard: Occupational exposure to methylene chloride. HEW Pub. No. 76-138. U.S. Dep. Health Edu. Welfare, Cincinnati, Ohio.

National Institute for Occupational Safety and Health. 1976b. Registry of toxic effects of chemical substances. HEW Pub. No. 76-191. U.S. Dep. Health Edu. Welfare, Rockville, Md.

National Library of Medicine. 1978b. Toxicity of halomethanes. Off-line bibliographic citation list generated by Medlars II, Toxline before 1975 and 1975-1978.

Occupational Safety and Health Administration. 1976. General industry standards. OSHA 2206, revised January, 1976. U.S. Dep. Labor, Washington, D.C.

Ohta, T., et al. 1976. Local distribution of chlorinated hydrocarbons in the ambient air in Tokyo. Atmos. Environ. 10: 557.

Owens, D.F., and A.T. Rossano. 1969. Design procedures to control cigarette smoke and other air pollutants. ASHPAE Trans. 75: 93.

Palmer, T.Y. 1976. Combustion sources of atmospheric chlorine. Nature 263: 44.

Patty, F.A. 1958. Industrial hygiene and toxicology. 2nd ed. Vol. I. Toxicology. Interscience Publishers, John Wiley and Sons, Inc., New York. (Cited in Natl. Acad. Sci., 1978).

Patty, F.A. 1963. Industrial hygiene and toxicology. 2nd ed. Vol. II. Toxicology. Interscience Publishers, John Wiley and Sons, Inc., New York.

Paulet, G., et al. 1975. Fluorocarbons and general metabolism in the rat, rabbit, and dog. Toxicol. Appl. Pharmacol. 34: 197.

Philippe, R.J., and M.E. Hobbs. 1956. Some components of the gas-phase of cigarette smoke. Anal. Chem. 28: 2002.

Pierotti, D., and R.A. Rasmussen. 1976. Interim report on the atmospheric measurement of nitrous oxide and the halocarbons. NASA Grant NSG 7214. Natl. Aeronautical Space Admin., Washington, D.C.

Pierotti, D., et al. 1976. Trip report on the cruise of the R/V Alpha Helix from San Diego, Calif., to San Martin, Peru. NSF Grant No. OCE 75-04688A03. Natl. Sci. Foundation, Washington, D.C.

Poirier, L.A., et al. 1975. Bioassay of alkylhalides and nucleoxide base analogs by pulmonary tumor response in Strain A mice. Cancer Res. 35: 1411.

Prendergast, J.A., et al. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane, and 1,1-dichloroethylene. Toxicol. Appl. Pharmacol. 10: 270.

Price, P.J., et al. 1978. Transforming activities of trichloroethylene and proposed Ind. alternatives. In Vitro 14: 290.

Quevauviller, A. 1965. Hygiene et securite des pulseurs pour aerosols medicamenteaux. Prod. Probl. Pharm. 20: 14.

Quevauviller, A., et al. 1964. Local tolerance in animals to chlorofluorinated hydrocarbons. Therapie 19: 247.

Rathus, E.M., and P.J. Landy. 1961. Methyl bromide poisoning. Br. Jour. Ind. Med. 18: 53.

Redford-Ellis, M., and A.H. Gowenlock. 1971a. Reaction of chloromethane with human blood. Acta Pharmacol. Toxicol. 30: 36.

Redford-Ellis, M., and A.H. Gowenlock. 1971b. Reaction of chloromethane with preparations of liver, brain, and kidney. Acta Pharmacol. Toxicol. 30: 49.

Riley, E.C., et al. 1966. Methylene chloride vapor in expired air of human subjects. Am. Ind. Hyg. Assoc. Jour. 27: 341.

Roehm, R.S., et al. 1943. Jour. Dairy Sci. 26: 205.

Rosenblum, I., et al. 1960. Chronic ingestion by dogs of methyl bromide-fumigated foods. Arch. Environ. Health 1: 316.

Salg, J. 1977. Cancer mortality rates and drinking water in 346 counties of the Ohio River Valley Basin. U.S. EPA Contract No. PO-5-03-4528-J. Ph.D. thesis. University of North Carolina.

Sanders, V.M., et al. 1977. Functional activity of the reticuloendothelial system (RES) in mice exposed to the halomethanes, drinking water contaminants. Submitted: Va. Jour. Sci. (Abstract.)

Savolainen, H., et al. 1977. Biochemical and behavioral effects of inhalation exposure to tetrachloroethylene and dichlormethane. Jour. Neuropathol. Exp. Neurol. 36: 941.

Sax, N.I. 1968. Dangerous properties of industrial materials. 3rd ed. Reinhold Book Corp., New York.

Sayer, R.R., et al. 1930. Toxicity of dichlorodiflouromethane. U.S. Bur. Mines Rep. R.I. 3013.

Schuller, G.B., et al. 1978. Effect of four haloalkanes on humoral and cell mediated immunity in mice. Presented Soc. Toxicol. Meet.

Schwetz, B.A., et al. 1975. The effect of maternally inhaled trichloroethylene, perchloroethylene, methyl chloroform, and methylene chloride on embryonal and fetal development in mice and rats. Toxicol. Appl. Pharmacol. 32: 84.

Scott, R. 1976. Household product safety. The Washington Post.

Scudamore, K.A., and S.G. Heuser. 1970. Residual free methyl bromide in fumigated commodities. Pestic. Sci. 1: 14.

Seo, S.T., et al. 1970. Residues of ethylene dibromide, methyl bromide, and ethylene chlorobromide resulting from fumigation of fruits and vegetables infested with fruit flies. Jour. Econ. Entomol. 63: 1093.

Shackelford, W.M., and L.H. Keith. 1976. Frequency of organic compounds identified in water. EPA-600/4-76-062. Environ. Res. Lab. U.S. Environ. Prot. Agency, Athens, Ga.

Shargel, L., and R. Koss. 1972. Determination of fluorinated hydrocarbon propellants in blood of dogs after aerosol administration. Jour. Pharmacol. Sci. 61: 1445.

Sherman, H. 1974. Long-term feeding studies in rats and dogs with dichlorodifluoromethane (Freon 12 Food Freezant). Unpubl. rep. Haskell Lab.

Shimkin, M.B., and G.D. Stoner. 1975. Lung tumors in mice: application to carcinogenesis bioassay. Adv. Cancer Res. 21: 1.

Sidwell, V.D., et al. 1974. Composition of the edible portion of raw (fresh or frozen) crustaceans, finfish, and mollusks. I. Protein, fat, moisture, ash, carbohydrate, energy value, and cholesterol. Mar. Fisheries Revies 36: 21.

Simmon, V.F. et al. 1977. Mutagenic activity of chemicals identified in drinking water. S. Scott, et al., eds. In Progress in genetic toxicology.

Simmonds, P.G., et al. 1974. Distribution of atmospheric halocarbons in the air over the Los Angeles basin. Atmos. Environ. 8: 209.

Singh, H.B., et al. 1977. Urban-non-urban relationships of halocarbons, SF_6, N_2O and other atmospheric constituents. Atmos. Environ. 11: 819.

Sivak, A. 1978. BALB flash C-3T3 neoplastic transformation assay with methylene chloride (food grade test specification). Rep. Natl. Coffee Assoc. Inc.

Slater, T.F. 1965. Relative toxic activities of tetrachloromethane and trichlorofluoromethane. Biochem. Pharmacol. 14: 178.

Smith, W.W., and W.F. von Oettingen. 1947a. The acute and chronic toxicity of methyl chloride: I. Mortality resulting from exposure to methyl chloride in concentrations of 4,000 to 300 ppm. Jour. Ind. Hyg. Toxicol. 29: 47.

Smith, W.W., and W.F. von Oettingen. 1947b. The acute and chronic toxicity of methyl chloride. I. Mortality resulting from exposure to methyl chloride in concentrations of 4,000 to 300 ppm. Jour. Ind. Hyg. Toxicol. 29: 47.

Smith, W.W., and W.F. von Oettingen. 1947c. The acute and chronic toxicity of methyl chloride. II. Symptomatology of animals poisoned by methyl chloride, Jour. Ind. Hyg. Toxicol. 29: 123.

Sokolova, I.P. 1972. Hygienic standardization of some fumigants in the air of ship chambers after gas treatment. Tr. Nauch. Konf., Nauch.-Issled. Inst. Gig. Vod. Transp. 2: 160.

Speizer, F.E., et al. 1975. Palpitation rates associated with fluorocarbon exposure in a hospital setting. New England Jour. Med. 292: 624.

Spevac, L., et al. 1976. Methyl chloride poisoning in four members of a family. Br. Jour. Ind. Med. 33: 272.

Stecher, P.G., et al. 1968. The Merck Index. 8th ed. Merck and Co., Inc., Rahway, N.J.

Stephens, S., et al. 1970. Phenotypic and genetic effects in *Neurospora crassa* produced by selected bases and gases mixed with oxygen. Dev. Ind. Microbiol. 12: 346.

Stewart, R.D., and C.L. Hake. 1976. Paint remover hazard. Jour. Am. Med. Assoc. 235: 398.

Stewart, R.D., et al. 1972a. Experimental human exposure to methylene chloride. Arch. Environ. Health 25: 342.

Stewart, R.D., et al. 1972b. Carboxyhemoglobin elevation after exposure to dichloromethane. Science 176: 295.

Stofen, D. 1973. Tolerance levels for toxic substances in drinking water. Stadtehyg. 24: 109. (Transl. by R. Mansfield, Oak Ridge Natl. Lab. ORNL-Tr-2975).

Stokinger, H.E., and R.L. Woodward. 1958. Toxicologic methods for establishing drinking water standards. Jour. Am. Water Works Assoc. 50: 515.

Stokinger, H.E., et al. 1963. Threshold limit values for 1963. Jour. Occup. Med. 5: 491.

Su, C., and E. Goldberg. 1973. Chlorofluorocarbons in the atmosphere. Nature 245: 27.

Su, C., and E. Goldberg. 1976. Environmental concentrations and fluxes of some halocarbons. In H.L. Windom and R.A. Duce, eds. Marine pollutant transfer. Lexington Books, D.C. Heath and Co., Lexington, Mass.

Symons, J.M., et al. 1975. National organics reconnaissance survey for halogenated organics. Jour. Am. Water Works Assoc. 67: 634.

Taylor, G.J., and R.T. Drew. 1975. Cardiomyopathy predisposes hamsters to trichlorofluoromethane. Submitted Toxicol. Appl. Pharmacol.

Taylor, G.J., and W.S. Harris. 1970. Glue sniffing causes heart block in mice. Science 170: 866.

Texas State Department of Health. 1957. Methyl bromide poisoning. Rep. No. OH-14, Div. Occup. Health., Texas.

Theiss, J.C., et al. 1977. Test for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in strain A mice. Cancer Res. 37: 2717.

Tourangeau, F.J., and S.R. Plamondon. 1945. Cases of exposure to methyl bromide vapours. Can. Jour. Publ. Health 36: 362.

Uehleke, H., and T. Warner. 1975. A comparative study of the irreversible binding of labeled halothane, trichlorofluoromethane, chloroform, and carbon tetrachloride to hepatic protein and lipids in vitro and in vivo. Arch. Toxicol. 34: 289.

Uehleke, H., et al. 1977. Metabolic activation of haloalkanes and tests in vitro for mutagenicity. Xenobiotica 7: 393.

Underwriters Laboratories. 1971. Comparative hazards of modern refrigerants. Data card No. UL5 and UL5-A.

U.S. EPA. 1975. Preliminary assessment of suspected carcinogens in drinking water, and appendices. A report to Congress, Washington, D.C.

U.S. EPA. 1976. Environmental hazard assessment report, major one- and two- carbon saturated fluorocarbons, review of data. EPA 560/8-76-003. Off. Toxic Subst. Washington, D.C.

U.S. EPA. 1977. Multimedia environmental goals for environmental assessment. Interagency energy-environment research and development program report. EPA 600/7-77-136a,b. Environ. Res. Lab., Research Triangle Park, N.C.

U.S. EPA. 1978a. Statement of basis and purpose for an amendment to the national interim primary drinking water regulations on trihalomethanes, January, 1978. Off. Water Supply, Washington, D.C.

U.S. EPA. 1978b. The National Organic Monitoring Survey. Rep. (unpubl.). Tech. Support Div., Off. Water Supply, Washington, D.C.

Van Stee, E.W., and K.C. Back. 1971. Brain and heart accumulation of bromotrifluoromethane. Rep. AD 721211. Natl. Tech. Inf. Serv., Springfield, Va.

Veith, G.D., et al. An evaluation of using partition coefficients and water solubility to estimate bioconcentration factors for organic chemicals in fish. (Manuscript).

Viner, N. 1945. Methyl bromide poisoning: New industrial hazard. Can. Med. Assoc. Jour. 53: 43.

Vitte, V.I., et al. 1970. Residual amounts of bromides in plant food products fumigated with methyl bromide and characteristics of their biological action. Gig. Primen., Toksikol. Pestits. Klin. Otravlenii 8: 386.

von Oettingen, W.F. 1955. The halogenated hydrocarbons: Toxicity and potential dangers. No. 414. U.S. Publ. Health Serv., Washington, D.C.

von Oettingen, W.F. 1964. The halogenated hydrocarbons of industrial and toxicological importance. Elsevier Publ. Co., Amsterdam.

von Oettingen, W.F., et al. 1949. Relation between the toxic action of chlorinated methanes and their chemical and physiochemical properties. Natl. Inst. Health Bull. No. 191.

von Oettingen, W.F., et al. 1950. Comparative studies of the toxicity and pharmacodynamic action of chlorinated methanes with special reference to their physical and chemical characteristics. Arch. Int. Pharmacodyn. Ther. 81: 17.

Vozovaya, M.A. 1974. Gynecological illnesses in workers of major industrial rubber products plants occupations. Gig. Tr. Sostoyanie Spetsificheskikh Funkts. Rab. Neftekhim. Khim. Prom-sti. (Russian) 56. (Abstract.)

Waritz, R.S. 1971. Toxicology of some commercial fluorocarbons. Rep. AD 751429. Natl. Tech. Inf. Serv. Springfield, Va.

Watanabe, T., and D.M. Aviado. 1975. Toxicity of aerosol propellants in the respiratory and circulatory systems. VII. Influence of pulmonary emphysema and anesthesia in the rat. Toxicology 3: 225.

Watrous, R.M. 1942. Methyl bromide: Local and mild systemic toxic effects. Ind. Med. 11: 575.

Weinstein, I.B. 1978. Current concepts on mechanisms of chemical carcinogenesis. Bull. N.Y. Acad. Med. 54: 366.

Weissbecker, L., et al. 1971. Cigarette smoke and tracheal mucus transport rate: Isolation of effect of components of smoke. Am. Rev. Resp. Dis. 104: 182.

Wilkness, P.E., et al. 1973. Atmospheric trace gases in the southern hemisphere. Nature 245: 45.

Wilkness, P.E., et al. 1975. Trichlorofluoromethane in the troposphere, distribution and increase, 1971 to 1974. Science 187: 832.

Williford, J.H., et al. 1974. Residual bromide in tissues of rats fed methyl bromide fumigated diets. Jour. Anim. Sci. 38: 572.

Wills, J.H. 1972. Sensitization of the heart to catecholamine-induced arrhythmia. Proc. 3rd Ann. Conf. Environ. Toxicol. AD Rep. No. 773766. U.S. Natl. Tech. Inf. Serv.

Winneke, G. 1974. Behavioral effects of methylene chloride and carbon monoxide as assessed by sensory and psychomotor performance. In Behavioral toxicology - Early detection of occupational hazards. Publ. No. (NIOSH) 74-126. U.S. Dep. Health Edu. Welfare.

Wolburg, I. 1973. The use of electroencephalography in industrial toxicology. Activ. Nerv. Super. (German) 15: 226. (Abstract.)

Wyers, H. 1945. Methyl bromide intoxication. Br. Jour. Ind. Med. 2: 24.